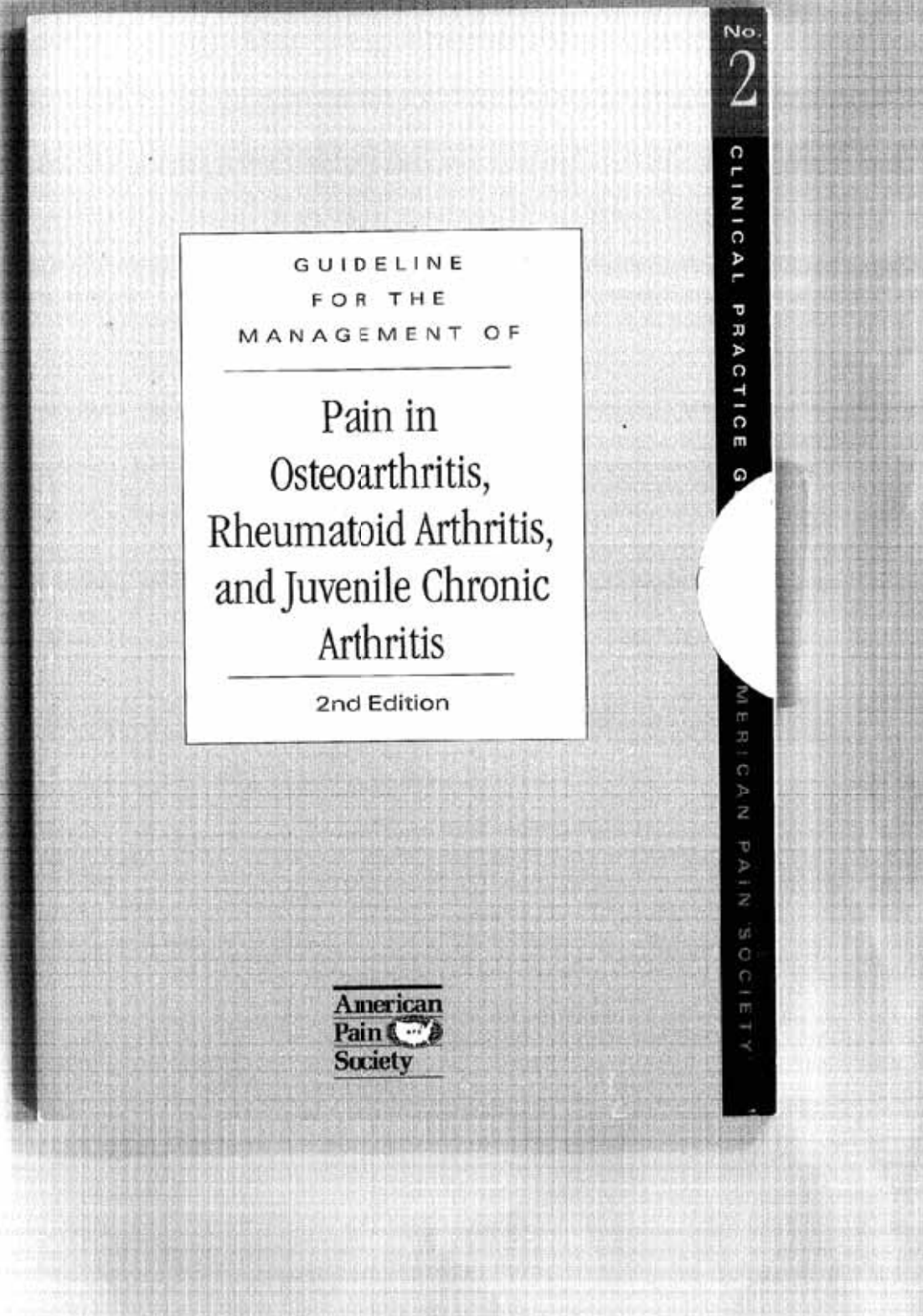


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We hope that you find this APS guideline to be a valuable resource.

Sincerely,

A handwritten signature in black ink, appearing to read "Dr. Robert Reder".

Dr. Robert Reder
V.P., Medical Affairs & Worldwide Drug Safety

A7264 3/03

Dedicated to Physician and Patient

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Many Colors, Many Feelings

By Issadora Sacteng

Down, down deep is how
I feel
on those deep dark blue
days.
Deep in the sea is where I
lay
for many unknown days.
Bright, rich red is how I
feel,
my muscles burn in the
fire,
the red so deep, it never
leaves
its color stains my pain
level forever.
Green, dark lonely green
I am caught in some
strange ressellation.
The color of motion,
the motion in my
stomach
that occurs many days is swampy and green.
Yellow, bright yellow
is the big warm sun
that beams down to thaw my stiff body
with a nice warm glow.
Florescent black strikes midnight with the clock seeping its sleepless poison.
These are the colors that I see
the colors that make up my dis' ease.



Issadora Sacteng was diagnosed with juvenile chronic arthritis (JCA) as a very young child. She has learned that chronic pain is hard for people to understand, including family, friends, and clinicians. She began to use her poetry as a way to cope with the pain and to help others understand how pain is experienced. As a child, she dreamed of the day that she would outgrow her arthritis, as many children with JCA do. Surprisingly to her, this has not happened, and she continues to struggle with chronic pain and arthritis flares as a young adult. About her artistic work, she says, "It seems that it was through my poetry that I could express my experience with pain. Writing poems and doing sketches helped me to cope with the ever-present chronic pain."

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GUIDELINE FOR THE
MANAGEMENT OF

Pain in
Osteoarthritis, Rheumatoid
Arthritis, and
Juvenile Chronic Arthritis

2nd edition

AMERICAN PAIN SOCIETY

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Glenview, IL 60025-1485

Simon, L., Lipman, A., Jacob, A., Caudill-Slosberg, M., Gill, L., Keefe, E., Kerr, K., Minor, M., Sherry, D., Vallerand, A., & Vasudevan, S. (2002). *Guideline for the Management of Arthritis Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*, APS Clinical Practice Guidelines Series, No 2. Glenview, IL: American Pain Society.

Any recommendations made by the authors must be weighed against the clinician's own clinical judgment, based on but not limited to such factors as the patient's condition, benefits versus risks of suggested treatment, and comparison with recommendations of pharmaceutical compendia and other authorities.

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Foreword

Arthritis is a generic term that describes more than 100 different, and usually painful, conditions, the most common of which is osteoarthritis, which affects from 16 million to 23 million Americans. More than 2.5 million Americans have rheumatoid arthritis, and 285,000 children have juvenile chronic arthritis. There currently is no cure for arthritis, though a few treatments can alter the natural history of the disease in some people.

Despite the recent advances in pain management, many people with arthritis experience levels of acute and chronic pain that affect their ability to function and reduce their quality of life. The recognition that undertreatment of pain in this population is common prompted the development of this evidence-based clinical practice guideline.

The American Pain Society (APS) is committed to improvement in the management and study of pain associated with many conditions. With the support of many professional organizations, corporations, and consumer groups, APS applies state-of-the-art methods to develop evidence-based guidelines and disseminate them broadly. The *Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease* was published in 1999, and an emergency department version of it was published in 2001. Guidelines now in preparation focus on pain related to cancer, fibromyalgia, and other conditions.

It is our sincerest hope that these guidelines will help improve clinical practice and advance pain-related research and education.

Michael A. Ashburn, MD MPH
President
American Pain Society

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Preface

The American Pain Society's (APS) Clinical Practice Guidelines Program (CPG) began in 1987 with publication of the first edition of *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* (APS, 1987), which is now in its fourth edition (1999). The *Guideline for the Management of Acute and Chronic Pain in Sickle-Cell Disease*, published in 1999, was the first APS evidence-based guideline. The *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis* is the second.

This clinical practice guideline is intended for use by physicians, nurses, and other healthcare professionals who work with adults who have osteoarthritis (OA) or rheumatoid arthritis (RA) of the extremities, or with children who have juvenile chronic arthritis (JCA), and for pain specialists unfamiliar with the dynamics of arthritis pain. After a brief description of OA, RA, and JCA and how they are managed, the discussion of treatment is limited to pain management. Because pain is a major cause of disability in people with arthritis, special consideration is given to the impact of pain management on functional status.

The guideline was developed by an interdisciplinary panel of experts in the management of arthritis pain. The panel combined scientific evidence review and expert judgment to develop recommendations for pain management. The guideline is based on the best evidence available at the time of writing. The science underlying pain management is emerging rapidly, however, and some recommendations may require modification as new evidence becomes available. Chapter II contains a description of the process and sources of evidence used in developing the guideline. The panel found other relevant guidelines, including the American College of Rheumatology's *Recommendations for the Medical Management of Osteo-arthritis of the Hip and Knee* (2000) and The American Geriatrics Society's *Guideline for the Management of Pain in Older Persons* (1998), useful in formulating some of the recommendations.

Funding was provided by corporate contributors to the APS Guidelines Program. We are grateful to them and to the many nurses, physicians, pharmacists, psychologists, and others who provided the panel with valuable reviews and suggestions. We hope that the guideline contributes to the much-needed improvement in the management of arthritis pain and provides a framework for future research.

Ada K. Jacox, PhD RN
Chair, Clinical Practice Guidelines Committee
American Pain Society

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Individuals involved in drafting clinical practice guidelines are charged by APS with the responsibility to develop objective, complete, and balanced guidelines. Financial relationships with commercial companies could conflict with the responsibility when the company's products or services are related to the subject of the guideline. To ensure the integrity of APS and the Clinical Practice Guidelines Program, all participants in the development of clinical practice guidelines must submit a Conflict of Interest Disclosure Form to APS prior to participation in any guideline development activity.

All members of the Arthritis Pain Management Guidelines Panel have submitted a Conflict of Interest Disclosure form, which has been reviewed by the APS Executive Director, who has determined that no conflict of interest exists with any individual panel member. In addition, panel members disclosed financial relationships with commercial companies to all other panel members during panel meetings.

Individual Panel members currently have or have had relationships with the following pharmaceutical or biotechnology companies during the past 3 years:

Lee S. Simon. Research grants: Amgen, BMS, GD Searle Pharmacia, HMR (Avantis), Lilly, Proctor & Gamble; Consultant: Abgenix,

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Arthur G. Lipman. Research grants Endo, Pharmacia; Consultant: Alza, Endo, Merck, Pharmacia, Purdue Pharma; Speaker's Bureau: Endo, Merck, Ortho-McNeil, Pharmacia, Purdue Pharma

Margaret Caudill-Slosberg. Stockholder: Merck and Co., Inc.; Speaker's Bureau: Purdue Pharma.

Lowell H. Gill. Contract with Stelcast Co.

Francis J. Keefe. Consultant: BioLacert

David D. Sherry. Speaker's Bureau: Amgen, Wyeth-Ayerst

April Hazard Vallerand. Research grant: Janssen Pharmaceutica; Speaker's Bureau: Janssen Pharmaceutica, Purdue Pharma, Elan Pharmaceuticals-Nursing Advisory Panel

Ada K. Jacox, Carol D. Spengler. APS consultants receive funding from the APS Guidelines Program Fund.

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I. Overview of Osteoarthritis, Rheumatoid Arthritis, Juvenile Chronic Arthritis, and Related Pain

Pain is a major determinant of quality of life for people with osteoarthritis (OA) and rheumatoid arthritis (RA), which affect more than 20 million and 2.5 million Americans, respectively (National Institutes of Health [NIH], 2001a, 2001b). Despite receiving appropriate treatment for the underlying disease, many people experience pain that impairs physical and psychological function. The goals of optimal care for people with OA and RA are to determine what can be done to slow or correct the underlying disorder and to identify pain as an issue to be addressed as soon as the disease is diagnosed.

Juvenile chronic arthritis (JCA) affects approximately 285,000 children in North America and may cause significant morbidity. The different developmental stages of children challenge the ability to assess and manage pain effectively. The kind of care and attention given to help alleviate their pain, especially procedural pain, can have lasting positive or negative effects. Assessment, treatment, and particularities of pain in children are addressed in Chapter V.

Research shows that the undertreatment of pain can have many serious negative consequences, including physiological effects associated with increased catabolic demands (Carr et al., 1992). These consequences include muscle breakdown, impaired healing, weakness, impaired respiratory effort, increased risk of pulmonary complications and thromboembolic events, increased sodium and water retention, inhibited gastrointestinal motility, and increased sympathetic autonomic stimulation, which may lead to hypertension, tachycardia, and tachypnea. Persistent pain may be associated with a decreased immune response, which may be clinically important in autoimmune diseases. Adverse psychosocial effects of chronic pain include anxiety, depression, hopelessness, anger, hostility, poor interpersonal relations, and, perhaps most disturbingly, suffering.

The fatigue, weakness, and stiffness that commonly accompany pain in people with RA and OA also contribute to a decreased quality of life. Fortunately, in recent years clinicians and researchers have learned much about effective ways to manage pain. This evidence-based guideline provides information about current approaches to the treatment of acute and chronic pain that can be used in the management of people with OA, RA of the extremities, or JCA. The guideline is based on available scientific evidence and expert judgment. The process used to develop the guideline is described in Chapter II.

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Pain Associated with Arthritis

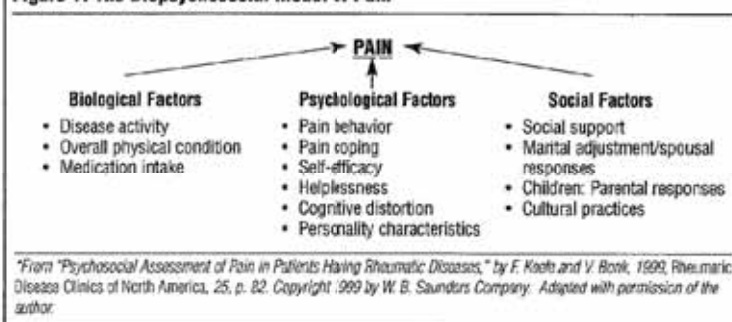
Pain is always a subjective experience. Each individual learns the meaning of the word "pain" through experiences related to injury in early life. Pain is an unpleasant sensation and therefore is also an emotional experience (Merskey, 1986).

Pain is a significant stressor for people with arthritis. Sometimes pain is viewed as an indication of disease activity (Ruzicka, 1998), even though disease activity/severity does not predict the intensity of pain or the level of function of the individual. People with arthritis describe their pain in different ways; "aching," however, is the term chosen most often to describe it (Papageorgiou & Badley, 1989). "Throbbing" and "stiffening" also are used. In RA, the pain experience often is most severe in the early and active stages of the disease before a successful treatment regimen is in place (Williams & Wood, 1988).

People with OA, RA, or JCA experience both acute and chronic pain. An NIH Conference on Pain (NIH, 1986) noted that "the single most useful method for evaluating acute pain...is to ask the person how he or she feels" (p. 4). Acute arthritic pain should be approached in the same manner as other acute pain by attempting to remove or modify the underlying cause, administering indicated analgesics, and reducing patients' fears that may exacerbate their pain.

Chronic pain is more complex than acute pain because it includes interactions among the biological, psychological, and social factors that influence pain and function. A biopsychosocial model (Figure 1) is useful in describing some of the factors that may influence how chronic pain is experienced by people with OA, RA, or JCA.

Figure 1. The Biopsychosocial Model of Pain*



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A primary consideration when managing chronic pain is the individual's level of function because this is influenced by physical and psychosocial factors and may be improved without complete pain relief. Many people with arthritis must learn to live with a disease that can profoundly affect their earning potential, function, and lifestyle. It is important to treat the patient as a whole person, using methods that enlist patients' enthusiasm for therapy and facilitate participation in their care. Although this guideline is focused primarily on pain and its management, it is useful to have a basic knowledge of OA, RA, and JCA and how they are managed. Accurate assessment and management of pain requires differentiation of the types and causes of pain and definition of treatment objectives.

Arthritis

Arthritis does not refer to a single disease; it is a generic term that describes more than 100 different conditions. The most common condition is OA, affecting from 16 million to 23 million Americans typically older than 60 years of age (National Institute on Aging [NIA], 1996; NIH, 2001a). Considering the cost of diagnosis; nonpharmacologic, pharmacologic, and surgical interventions; side effects of medications; and lost productivity, arthritis is one of the most expensive and debilitating diseases in the United States (Gabriel & Matteson, 1995; NIA).

There are no treatments that cure and few that alter the natural history of arthritis, while at the same time the therapy typically prescribed has the potential for important toxicity. Consistent with a biopsychosocial approach, pharmacologic and nonpharmacologic therapies (e.g., occupational, physical therapy, cognitive-behavioral), accompanied by patient education, are all important components of a treatment plan for pain associated with arthritis. Education about the disease and the rationale for therapy may enhance patients' adherence to the therapeutic regimen. Patients should participate in establishing treatment goals and be informed about the risks and benefits of therapy and its functional impact.

Osteoarthritis

OA is a disease most often seen in older individuals, but it also may occur in younger people following injury or repetitive stress. More than 80% of people older than 75 have clinical OA, and more than 80% over the age of 50 have radiologic evidence of OA (Sharma, 2001).

Pathophysiology

The joint consists of bone, cartilage, and connective tissue (Figure 2). Subchondral bone is covered by hyaline or articular cartilage that consists of

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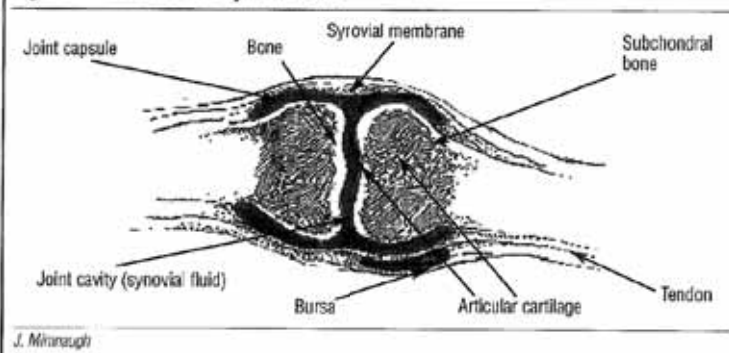
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type II collagen, chondrocytes, and proteoglycans (i.e., high molecular weight glycoproteins that retain water and thereby increase resiliency of the cartilage). The arcade arrangement of the collagen fibrils provides tensile strength, and the proteoglycans provide distensibility by retaining adequate hydration. The synovial cell layer that lines the joint produces a viscous synovial fluid that lubricates joint motion. Superficial to the synovial membrane is a flexible joint capsule with ligaments and tendons. In strategic spots outside the joint itself, bursae provide a smooth surface for muscle, tendon, and ligaments to pass over roughened bone surfaces. These joint components provide for both motion and load bearing across nearly frictionless surfaces, and any or all of these joint components are involved in the osteoarthritic process depending on the extent of the disease.

Figure 2. Structure of a Synovial Joint



OA is primarily a disease of the cartilage that progressively produces a local tissue response, mechanical change, and failure of function. The disease typically affects weight-bearing joints asymmetrically. Historically, OA was not considered an inflammatory process, which led to it being termed a degenerative joint disease. More recently an association has been established between OA and typically local low-grade inflammation with few systemic effects (Brandt, 1995; Ryu, Treadwell, & Mankin, 1984). The osteoarthritic process can result from excessive or repetitive loading of the normal joint, including work-related repetitive activities that damage cartilage or subchondral bone, trauma, or increased load to the joint from chronic obesity. This process may occur in the context of either

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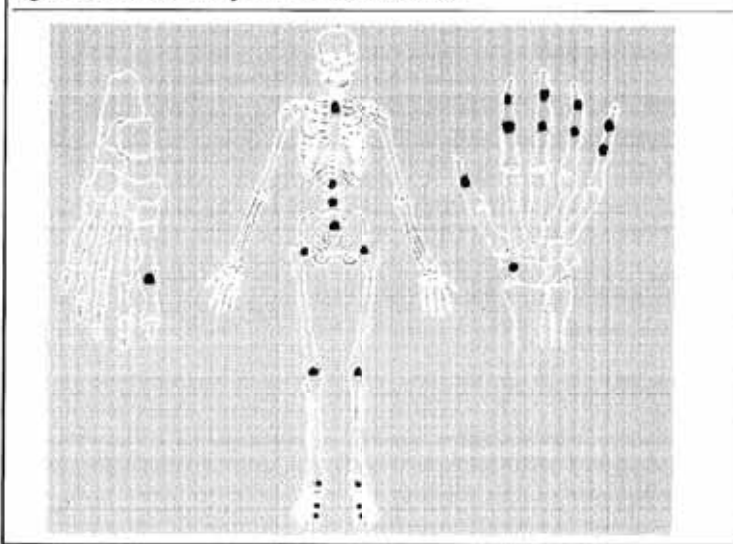
inherently abnormal cartilage or of a specific insult to the structure of cartilage, leading to increased susceptibility.

As cartilage is damaged, it becomes thinner, develops fissures or large clefts, and proteoglycan synthesis decreases. That process leads to further decreased cartilaginous load-bearing capacity. The chondrocyte in cartilage can respond initially by attempting to repair its surrounding extracellular matrix, but as it is overwhelmed there is increased release of neutral metalloproteinases and lysosomal proteases leading to further matrix loss and ultimately increasing the destructive cascade.

Presentation of Osteoarthritis

The joints most commonly involved in OA include knees, hips, feet, ankles, the distal interphalangeal (DIP) joints, the proximal interphalangeal (PIP) joints, the first carpometacarpal joints, the cervical spine, and the lower spine (Figure 3). Involvement of the wrists, elbows, and shoulders is uncommon unless there is trauma to those areas or the patient has generalized OA. Typically, people describe feeling stiffness (a result of soft tissue reaction to change in the physical and mechanical properties of joints) in the involved joints when arising in the morning, with the symptoms lasting no longer than 20–30 minutes. While

Figure 3. Joints Commonly Involved in Osteoarthritis



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sitting or driving, people may experience a "gel" phenomenon, which is described as a feeling of stiffness that disappears when the person begins to move again. This gel phenomenon lasts no longer than 20 minutes or so. If the symptoms of morning stiffness or the gel phenomenon last longer, there may be more joint inflammation than is normally associated with OA, and other diagnoses should be considered. Morning stiffness improves with the use of the joints, but most people experience increased pain as the joints continue to bear weight throughout the day.

The diagnosis of OA is based largely on clinical presentation and physical findings. Radiographic evaluation can be useful, but blood tests are not. Although local inflammation may be present, erythrocyte sedimentation rate (ESR), hematocrit, and white blood cell (WBC) counts are normal. Radiographs commonly reveal joint space narrowing, increased subchondral bony sclerosis, and sometimes subchondral cyst formation and osteophytes. Small synovial effusions are typically noninflammatory or minimally inflammatory; typically WBC counts are less than 2,000, and most cells are mononuclear.

Rheumatoid Arthritis

RA, the second most common form of arthritis, is a destructive and commonly debilitating systemic inflammatory disease. It affects women more frequently than men (5:1), has a peak incidence between the ages of 20 and 50 years, and a prevalence of 1%–2% of adults, ranging from 0.3% of the population younger than 35 years to about 10% of those older than 65 years (Harris & Zorab, 1997). It is a chronic autoimmune disorder characterized by symmetrical synovitis of the joints involving typically small and large diarthrodial joints and leading to progressive destruction. It is heterogeneous in nature with variable disease expression and is often associated with the formation of serum rheumatoid factor. A small number of patients have extremely mild disease associated with spontaneous remission, although most suffer unremitting or intermittent disease progression. The importance of treating RA earlier and more aggressively, before cartilage destruction occurs, was emphasized by the Centers for Disease Control and Prevention (CDC, 1999; Marwick, 1999).

Pathophysiology

The disease begins in the synovium (i.e., tissue lining the joint) and systemic extra-articular manifestations may include fever, weight loss, skin thinning, scleritis, corneal ulcers, and the formation of subcutaneous or subperiosteal nodules. Multiple organs may be involved, leading to premature death. The etiology of RA is unknown. Possibilities include various viral or bacterial infections such as Epstein-Barr virus or infection with certain mycobacteria. An environmental event, perhaps viral particles or bacterial proteins, stimulates an immune

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response in the appropriate genetic host leading to a host immune response that may cross react with similar antigens in the host joint tissue. There are other possible explanations of the environment interacting with the appropriate host.

When dendritic cells, monocytes, and macrophages are activated by the autoimmune process, they interact with and present antigen to the appropriate T cells. A series of events ensues that leads to the further activation of more monocytes and macrophages, T cells, B cells, and increased endothelial cell activity. These events increase the synthesis of adhesion molecules, leading to increased vascular margination of mononuclear cells. Polymorphonuclear cells are attracted to the inflamed joint fluid by the elaboration of multiple cytokines, some of which act as chemoattractants that increase delivery of inflammatory cells to the synovium and synovial fluid. Cytokines such as IL-1 α or β , IL-8, tumor necrosis factor (TNF)- α , platelet-derived growth factor (PDGF), heparin-binding growth factor (HBGF), GM-CSF, IFN- γ , TGF- β , IL-2, and IL-6 lead to increased activation of fibroblastlike cells in the synovium and chondrocytes, as well as other macrophages. The activation releases increased amounts of prostaglandins, neutral proteinases such as collagenases, stromelysin, and recruits osteoclast precursors, which culminate in the destruction of bone and cartilage by the invading proliferative synovium.

Fundamentally, RA is a progressive destructive inflammatory disease of the synovium that may be induced by some "arthro-tropic" virus or bacteria in the appropriate host with the correct HLA DR4 or DR1 alleles. This induction leads to the release of cytokines and other pro-inflammatory mediators and proteinases that ultimately participate in the destruction of the joint.

Presentation of Rheumatoid Arthritis

RA is a systemic inflammatory disease that occurs in people younger than those affected by OA. Patients may present with pain, swelling, warmth, and tenderness in various joints. Patients may experience the gel phenomenon and typically experience morning stiffness, which may last several hours or the entire day. Many people suffer from afternoon fatigue and require rest for about an hour each day. Fever and weight loss are common. Extra-articular manifestations can affect many organ systems (except for the kidneys unless vasculitis supervenes).

Symmetrical involvement of small and large joints is typical (Figure 4). This pattern differs from OA, which is characterized by asymmetrical involvement of the large weight-bearing joints. Progressive destruction of a joint, leading to loss of mechanical function and consequent disability in performing even the essential activities of daily living, occurs in people with RA who are not treated or who are unresponsive to therapy.

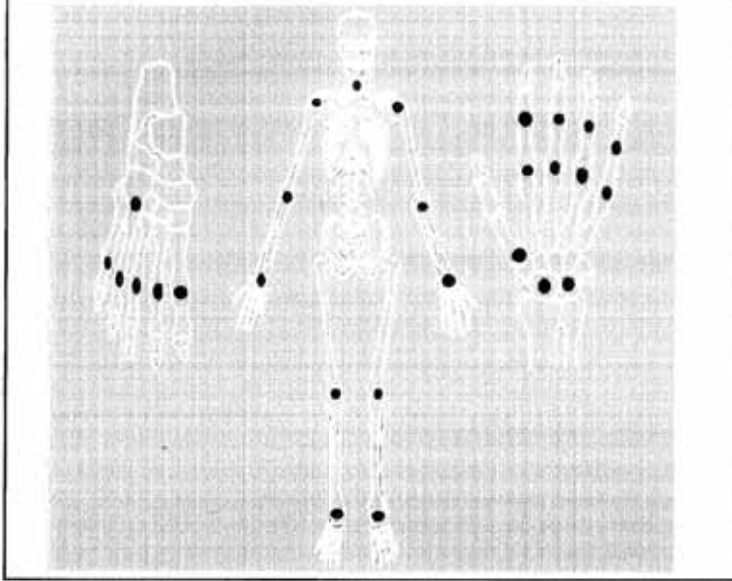
The diagnosis is based largely on history and a physical examination that reveals chronic progressive systemic inflammation with joint swelling, synovitis,

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Figure 4. Joints Commonly Involved in Rheumatoid Arthritis

warmth and tenderness, and, at times, large synovial effusions characterized by large numbers of polymorphonuclear (PMN) cells (approximating WBCs of 20,000–50,000 with 50%–70% PMNs), some mononuclear cells, poor viscosity, and no crystals. Subcutaneous or subperiosteal nodules occur on extensor surfaces or pressure points. Laboratory evidence includes elevation of acute phase reactants such as ESR or C-reactive protein. A progressive normocytic (or less commonly microcytic) anemia of chronic inflammatory disease, or a falling serum albumin, is a sign of a poor prognosis and may suggest evidence of endstage disease or emerging vasculitis. Other laboratory tests may be suggestive of extra-articular organ involvement. More than 90% of patients have rheumatoid factors in their blood and generalized polyclonal hypergammaglobulinemia. Thrombocytosis may be prominent.

Radiographic abnormalities are variable and depend on the duration of the disease. Early in RA there may be juxta-articular osteoporosis due to local inflammation and very small early erosions that can be identified only by special magnetic resonance imaging (MRI) studies. Subsequently, even traditional radiographs reveal progressive marginal joint erosions, cartilage loss evidenced by

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joint space narrowing, and lack of attempts at repair. When these changes symmetrically affect the wrists, the metacarpophalangeal and the PIP joints while sparing DIP joints, the probable diagnosis is RA or one of its variants.

Management of Osteoarthritis and Rheumatoid Arthritis

The primary therapy for arthritis of almost any type includes pharmacologic approaches, education, general nonpharmacologic measures such as rehabilitation therapy, and support. The establishment of effective patient-clinician relationships is crucial for effective therapy. People with OA or RA should become educated healthcare consumers and understand the importance of adequate rest and judicious exercise in conjunction with appropriate pharmacotherapy. They should understand the importance of adherence to the treatment regimen and be empowered by their clinicians so that they do not feel victimized by the disease or its therapy. An arthritis self-help course can reduce patients' perception of pain by an average of 20% (Kruger, Helmick, Callahan, & Haddix, 1998). It is essential for optimal management that clinicians ascertain and address the various biological, psychological, and social contributions to patients' pain.

No specific pharmacologic therapies have yet been found to cure or alter the disease process of OA. Therefore, analgesic, antiinflammatory medications, or both are the principal pharmacotherapies for people with OA.

RA pain often is most effectively managed in the long term by altering the natural history of the active progressive disease by using disease-modifying antirheumatic drugs, but analgesics and antiinflammatory drugs also have an important place in pain management.

More detailed discussions of pain management are presented in Chapter IV.

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II. Methods for Guideline Development

The guideline development process combined the review of available scientific evidence and the judgment of pain experts. A comprehensive literature review was conducted to locate recently published systematic evidence reviews and to identify areas in which new reviews were needed. This evidence was used in the development of the guideline.

The interdisciplinary panel comprised 10 experts in various aspects of the management of arthritis pain. Multiple drafts of the document were prepared by the panel and American Pain Society (APS) staff. Two drafts of the guideline underwent peer review, with 63 reviewers participating in the first review and 51 in the second. Peer reviewers are listed in Appendix D, except for those who chose to remain anonymous. The questionnaire that reviewers used to evaluate the drafts was based on the Institute of Medicine's *Guidelines for Clinical Practice: From Development to Use* (Field & Lohr, 1992).

Evidence Reviews

Four sources of evidence review were used: (a) Cochrane Collaboration Reviews, (b) other published systematic reviews, (c) reviews commissioned by APS, and (d) reviews conducted by APS panel and staff members. The Cochrane and other published reviews are listed in Tables 1 and 2.

Of the reviews commissioned by APS, three were completed under the direction of Linda Tyler, PharmD, at the University of Utah Health Sciences Center. One was of the cyclooxygenase-2 selective nonsteroidal antiinflammatory drugs (Table 3). The second was a review of the effects of unrelieved pain on the immune system, and the third the effects of opioids on the immune system. The latter two reviews are not summarized in this guideline. One review of opioids used in the treatment of osteoarthritis and rheumatoid arthritis pain was conducted by Peter Tugwell, MD, University of Toronto, chair of the Cochrane Musculoskeletal Group (Table 4). The remaining six reviews were conducted by APS panel and staff members and are listed in Table 5. All reviews conducted by APS staff and by the Utah Drug Information Service used the same protocol for reviewing individual studies.

The databases, dates searched, and review methods are described in each evidence review. For reviews conducted by the Utah Drug Information Service and APS panel and staff members, the following databases and dates were included: MEDLINE (1966–2001), CINAHL (1982–2001), Embase (1988–2001), PubMed (1966–2001), Healthstar (1975–2000), Current Contents (2000–2001), Web of Science (1980–2001), PsychInfo (1887–2001), Science Citation Indexes (1996–2001), and Cochrane database (1993–2001). The abstracts were searched to identify research articles. Case reports, letters to the

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Table 1. Published Systematic Evidence Reviews on Pain Management in Osteoarthritis

Cochrane Collaboration Reviews: OA	
Analgesics NSAIDs— nonselective	Towheed, T., Shea, B., Wells, G., & Hochberg, M. (2000). Analgesia and non-aspirin, non-steroidal anti-inflammatory drugs for osteoarthritis of the hip. <i>Cochrane Database Systematic Review</i> (2), CD000517. Watson, M.C., Brookes, S.T., Kirwan, J.R., & Faulkner, A. (2001). Non-aspirin, non-steroidal anti-inflammatory drugs for treating osteoarthritis of the knee. <i>Cochrane Database Systematic Review</i> (3), CD000142.
Dietary Supplements Glucosamine sulfate	Towheed, T.E., Anastassiades, T.P., Shea, B., Houpt, J., Welch, V., & Hochberg, M.C. (2001). Glucosamine therapy for treating osteoarthritis. <i>Cochrane Database Systematic Review</i> (3), CD002946.
Herbal therapy	Little, C.V., Parsons, T., & Logan, S. (2001). Herbal therapy for treating osteoarthritis. <i>Cochrane Database Systematic Review</i> (3), CD002947.
Physical Modalities TENS	Osiri, M., Welch, V., Brosseau, L., Shea, B., McGowan, J., Tugwell, P., & Wells, G. (2001). Transcutaneous electrical nerve stimulation for knee osteoarthritis. <i>Cochrane Database Systematic Review</i> (3), CD002823.
Laser therapy	Brosseau, L., Welch, V., Wells, G., deBie, R., Gam, A., Harman, K., Morin, M., Shea, B., Tugwell, P. (2001). Low level laser therapy (Classes I, II and III) for treating osteoarthritis. <i>Cochrane Database Systematic Review</i> (3), CD002046.
Balneotherapy	Verhegen, A.P., de Jot, H.C.W., de Bio, R.A., Kessels, A.G.H., Boers, M., & Knipschild, P.G. (2001). Balneotherapy for rheumatoid arthritis and osteoarthritis. <i>Cochrane Database Systematic Review</i> (3), CD000518.
Ultrasound	Welch, V., Brosseau, L., Peterson, J., Shea, B., Tugwell, P., Wells, G. (2001). Therapeutic ultrasound for osteoarthritis of the knee. <i>Cochrane Database Systematic Review</i> (3), CD003132.
Other Published Systematic Reviews: OA	
Analgesics NSAIDs— nonselective	Moore, R.A., Tramer, M.R., Carroll, D., Wiffen, P.J., & McQuay, H.J. (1998). Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. <i>British Medical Journal</i> , 316, 333-338. Riedemann, P.J., Bersinic, S., Cuddy, L.J., Torrance, G.W., & Tugwell, P.X. (1993). A study to determine the efficacy and safety of tenoxicam versus piroxicam, diclofenac and indomethacin in patients with osteoarthritis: A meta-analysis. <i>Journal of Rheumatology</i> , 20, 2095-2103. Superio-Cabuslay, E., Ward, M.M., & Lorig, K.R. (1996). Patient education interventions in osteoarthritis and rheumatoid arthritis: A meta-analytic comparison with nonsteroidal antiinflammatory drug treatment. <i>Arthritis Care and Research</i> , 9(4), 292-301. Towheed T.E., Hochberg M.C. (1997). A systematic review of randomized controlled trials of pharmacological therapy in osteoarthritis of the knee, with an emphasis on trial methodology. <i>Seminars in Arthritis and Rheumatism</i> 26(5), 755-770.

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Table 1. (cont.) Published Systematic Evidence Reviews on Pain Management in Osteoarthritis

Topical Agents	Moore, R.A., Truett M.R., Carroll, D., Wiffen, P.J., & McQuay, H.J. (1998). Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. <i>British Medical Journal</i> , 316, 333-338. Zhang, W.Y., & Li Win Po, A. (1994). The effectiveness of topically applied capsaicin: A meta-analysis. <i>European Journal of Clinical Pharmacology</i> 46, 517-522.
Antidepressants	Fishbain, D. (2000). Evidence-based data on pain relief with antidepressants. <i>Annals of Medicine</i> , 32, 305-316.
Dietary Supplements	
Glucosamine sulfate	Glucosamine and arthritis. (1997). <i>Bandolier</i> , 4(12), 1-3.
Chondroitin	McAlindon, T.E., LaValley, M.P., Gulin, J.P., & Felson, D.T. (2000). Glucosamine and chondroitin for treatment of osteoarthritis: A systematic quality assessment and meta-analysis. <i>Journal of the American Medical Association</i> , 283, 1459-1475.
Physical Modalities	
Diathermy	Marks, R., Ghassemi, M., Duarte, R., & Van Nguyen, J.P. (1999). A review of the literature on shortwave diathermy as applied to osteoarthritis of the knee. <i>Physiotherapy</i> 85, 304-316.
Laser therapy	Marks, R., & de Palma, E. (1999). Clinical efficacy of low power laser therapy in osteoarthritis. <i>Physiotherapy Research International</i> 4(2), 141-157.
Exercise therapy	La Mantia, K., & Marks, R. (1995). The efficacy of aerobic exercises for treating osteoarthritis of the knee. <i>New Zealand Journal of Physiotherapy</i> , 23(2), 23-30. Van Baar, M.E., Assendelft, W.J.J., Dekker, J., Oostendorp, R.A.B., & Bijlsma, J.W. (1999). Effectiveness of exercise therapy in patients with osteoarthritis of the hip or knee: a systematic review of randomized clinical trials. <i>Arthritis and Rheumatism</i> , 42, 1361-1369.
Patient Education	Superio-Cabuslay, E., Ward, M.M., & Lorig, K.R. (1995). Patient education interventions in osteoarthritis and rheumatoid arthritis: A meta-analytic comparison with nonsteroidal antiinflammatory drug treatment. <i>Arthritis Care and Research</i> , 9(4), 292-301.
Cognitive-Behavioral	Morley, S., Eccleston, C., & Williams, A. (1999). Systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy and behavior therapy for chronic pain in adults, excluding headache. <i>Pain</i> , 80, 1-13.

editor, articles describing diagnostic techniques, animal studies, and surveys reporting the incidence of pain were excluded. Published studies were reviewed and evaluated following a specific protocol.

Because of the large amount of evidence reviewed and summarized, it is not possible to include references to all studies in this guideline. An expanded description of the review processes and the APS reviews are published in a separate report (*Guideline Report for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis*, 2002) available from APS for a fee upon request.

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Table 2. Published Systematic Evidence Reviews on Pain Management in Rheumatoid Arthritis

Cochrane Collaboration Reviews	
Analgesics	
NSAIDs—nonselective	Gotzsche, P.C., & Johansen, H.K. (2001). Short-term low-dose corticosteroids vs. placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> (3), CD000189.
Intra-articular glucocorticosteroids	Criswell, L. A., Saag, K. G., Serns, K. M., Welch, V., Shea, B., Wells, G., & Suarez-Almazor, M. E. (2000). Moderate-term, low-dose corticosteroids for rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> (2), CD001158.
	Gotzsche PC, Johansen HK. (2001). Short-term low-dose corticosteroids vs placebo and nonsteroidal antiinflammatory drugs in rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000189.
DMARDs	Clark, P., Tugwell, P., Bennet, K., Bombardier, C., Shea, B., Wells, G., & Suarez-Almazor, M.E. (2001). Injectable gold for rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000520.
	Suarez-Almazor, M.E., Belseck, E., Shea, B., Homik, J., Wells, G., & Tugwell, P. (2001). Antimalarials for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000959.
	Suarez-Almazor, M.E., Belseck, E., Shea, B., Wells, G., & Tugwell, P. (2001). Cyclophosphamide for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD001157.
	Suarez-Almazor, M.E., Belseck, E., Shea, B., Wells, G., & Tugwell, P. (2001). Methotrexate for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000957.
	Suarez-Almazor, M.E., Belseck, E., Shea, B., Wells, G., & Tugwell, P. (2001). Sulfasalazine for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000958.
	Suarez-Almazor, M.E., Spooner, C., Belseck, E. (2000) Penicillamine for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD001460.
	Suarez-Almazor, M.E., Spooner, C.H., Belseck, E., & Shea, B. (2000). Auranofin versus placebo in rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (2), CD002048.
	Suarez-Almazor, M.E., Spooner, C., & Belseck, E. (2001). Azathioprine for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000959.
	Wells, G., Hagenauer, D., Shea, B., Suarez-Almazor, M.E., Welch, V.A., & Tugwell, P. (2001) Cyclosporine for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD001083.
Dietary Supplements	
Herbal therapy	Little, C., & Parsons, T. (2001) Herbal therapy for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD002948.
Physical Modalities	
Laser therapy	Brosscau, L., Welch, V., Wells, G., deBie, R., Gam, A., Harman, K., Morin, M., Shea, B., & Tugwell, P. (2001). Low level laser therapy (Classes I, II and III) for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD002049.

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Table 2. (cont.) Published Systematic Evidence Reviews on Pain Management in Rheumatoid Arthritis

Thermotherapy	Weich, V., Brosseau, L., Shea, B., McGowan, J., Wells, G., & Tugwell, P. (2001). Thermotherapy for treating rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD002826.
Balneotherapy	Verhagen, A.P., de Vet, H.C.W., de Bie, R.A., Kessels, A.G.H., Boers, M., & Knipschild, P.G. (2001). Balneotherapy for rheumatoid arthritis and osteoarthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000518.
Exercise	Van den Ende, C.H.M., Vliet Vlieland, T.P.M., Munneke, M., Hazes, J.M.W. (2001). Dynamic exercise therapy for rheumatoid arthritis. <i>Cochrane Database Systematic Review</i> , (3), CD000322.
Other Published Systematic Reviews	
Analgesics NSAIDs— nonselective	<p>Gotzsche, P.C. (1990). Sensitivity of effect variables in rheumatoid arthritis: A meta-analysis of 130 placebo controlled NSAID trials. <i>Journal of Clinical Epidemiology</i>, 43, 1313–1318.</p> <p>Moore, R.A., Tramer, M.R., Carroll, D., Wiffen, P.J., & McQuay, H.J. (1998). Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. <i>British Medical Journal</i>, 316, 333–338.</p> <p>Superio-Cabuslay, E., Ward, M.M., & Long, K.R. (1996). Patient education interventions in osteoarthritis and rheumatoid arthritis: A meta-analytic comparison with nonsteroidal antiinflammatory drug treatment. <i>Arthritis Care and Research</i>, 9(4), 292–301.</p>
Topical Agents	<p>Moore, R.A., Tramer, M.R., Carroll, D., Wiffen, P.J., & McQuay, H.J. (1998). Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. <i>British Medical Journal</i>, 316, 333–338.</p> <p>Zhang, W.Y., & Li Wei Po, A. (1994). The effectiveness of topically applied capsaicin: A meta-analysis. <i>European Journal of Clinical Pharmacology</i>, 46, 517–522.</p>
Antidepressants	Fishbain, D. (2000). Evidence-based data on pain relief with antidepressants. <i>Annals of Medicine</i> , 32(5), 305–316.
Combination Therapy	Verhoeven, A.C., Boers, M., & Tugwell, P. (1996). Combination therapy in rheumatoid arthritis: Updated systematic review. <i>British Journal of Rheumatology</i> , 37, 612–619.
Patient Education	Superio-Cabuslay, E., Ward, M.M., & Long, K.R. (1996). Patient education interventions in osteoarthritis and rheumatoid arthritis: A meta-analytic comparison with nonsteroidal antiinflammatory drug treatment. <i>Arthritis Care and Research</i> , 9(4), 292–301.
Cognitive-Behavioral	Morley, S., Eccleston, C., & Williams, A. (1999). Systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy and behavior therapy for chronic pain in adults, excluding headache. <i>Pain</i> , 80, 1–13.
Other	ter Riet, G., de Craen, A.J., de Boer, A., & Kessels, A.G. (1998). Is placebo analgesia mediated by endogenous opioids? A systematic review. <i>Pain</i> , 76, 273–275.

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Table 3. Studies of COX-2 Selective NSAIDs in Patients with Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Bensen et al., 1999	RCT	Placebo	203	The celecoxib and naproxen groups were similar in improvement from baseline global assessments, pain intensity, joint stiffness pain, physical function, and daily activities. The celecoxib 100 mg dose was less effective than the other celecoxib and naproxen groups. No significant difference in GI-related ADRs was seen among the celecoxib, naproxen, and placebo groups.
		Celecoxib 100 mg	203	
		Celecoxib 200 mg	197	
		Celecoxib 400 mg	202	
		Naproxen 1,000 mg	198	
		Treatment = 12 weeks		
Cannon et al., 2000	RCT	Rofecoxib 12.5 mg	259	All groups showed significant improvement from baseline in the assessment of disease status, therapy response, and arthritis pain when walking. Results were similar among the groups. All safety outcomes were similar among the groups (outcome, intensity, incidence of ADRs including blood pressure and laboratory values).
		Rofecoxib 25 mg	257	
		Diclofenac 150 mg	268	
		Treatment = 52 weeks		
Day et al., 2000	RCT	Placebo	74	Rofecoxib was similar to ibuprofen in the outcome pain walking on a flat surface, while rofecoxib was significantly better for patient assessment of response to therapy and physician global assessment of disease than ibuprofen. More patients withdrew from therapy due to ADRs in the ibuprofen group vs. the rofecoxib 12.5 mg, rofecoxib 25 mg, and placebo groups (8.4% vs. 4.1%, 3.7%, and 1.4%).
		Rofecoxib 12.5 mg	244	
		Rofecoxib 25 mg	242	
		Ibuprofen 2,400 mg	249	
		Treatment = 6 weeks		

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Table 3. (cont.) Studies of COX-2 Selective NSAIDs in Patients with Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Sirinich et al., 1999	RCT	Placebo	72	Rofecoxib 25 mg and 125 mg daily was significantly better than placebo for the primary outcome mean change in assessment of arthritis pain. No differences were seen between the rofecoxib groups in any other secondary efficacy outcomes. The overall incidences of ADRs were similar with rofecoxib 25 mg vs. placebo, although a difference was seen in the rofecoxib 125 mg vs. placebo (56.8% vs. 44.4%). The intensity and outcomes of the ADRs were similar in each group.
		Rofecoxib 25 mg	73	
		Rofecoxib 125 mg	74	
		Treatment = 6 weeks		
Hawkey et al., 2000	Pooled results from two RCTs	Placebo	371	At 24 weeks, ibuprofen had a significantly higher incidence of gastroduodenal ulcers (mucosal break ≥ 3 and ≥ 5 mm with unequivocal depth) than rofecoxib or placebo.
		Rofecoxib 25 mg	390	
		Rofecoxib 50 mg	379	
		Ibuprofen 2400 mg	376	
		Treatment = 16-24 weeks		

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Table 3. (cont.) Studies of COX-2 Selective NSAIDs in Patients with Arthritis*				
Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Laine et al., 1999	RCT	Placebo	177	At 24 weeks, ibuprofen had a significantly higher incidence of gastroduodenal ulcers (mucosal break ≥ 3 and ≥ 5 mm with unequivocal depth) than rofecoxib or placebo. Ibuprofen also was reported to have a significantly higher incidence of gastric duodenal ulcers than rofecoxib or placebo. The number of ulcers reported was lower in the rofecoxib and placebo vs. ibuprofen groups (10, 10, 18 vs. 52). The author calculated that if 2.8 patients were treated with rofecoxib 25 mg rather than with ibuprofen, one ulcer would be prevented for the first 6 months of therapy.
		Rofecoxib 25 mg	195	
		Rofecoxib 50 mg	186	
		Ibuprofen 2400 mg	184	
		Treatment = 16-24 weeks		
Langman et al., 1999	Combined analysis of eight RCTs	Rofecoxib group	Rofecoxib group	The total patient-years of exposure was 1,428 years for the rofecoxib group and 615 years for the NSAID group. The 12-month cumulative incidence of PUBs was lower in rofecoxib = 1.3% vs. NSAID = 1.8%. Confirmed PUBs were seen at 6 weeks and continued until 12 months. The 12-month cumulative incidences of withdrawals due to GI ADRs were lower in rofecoxib = 5.7% vs. NSAID = 7.8%.
		Rofecoxib 12.5 mg	1,209	
		Rofecoxib 25 mg	1,603	
		Rofecoxib 50 mg	545	

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Table 3. (cont.) Studies of COX-2 Selective NSAIDs in Patients with Arthritis*				
Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Zhao et al., 1999	RCT	NSAID group	NSAID group	All groups had significantly better functional status than the placebo group as measured by the Western Ontario and McMaster Universities Osteoarthritis Index. The incidences of serious ADRs were similar in each group. Two serious GI ADRs occurred in the naproxen group (1 case of gastric ulcer, 1 case of GI hemorrhage).
		Diclofenac 150 mg	590	
		Ibuprofen 2,400 mg	647	
		Nabumetone 1,500 mg	127	
		Treatment duration depended on study		
		6 weeks		
		6 weeks plus extension of 6 months		
		6 weeks plus up to 2 years of extensions		
		6 months		
		1 year plus extension of 1 year		
		Placebo	204	
		Celecoxib 100 mg	203	
		Celecoxib 200 mg	197	
		Celecoxib 400 mg	202	
		Naproxen 1,000 mg	198	
		Treatment = 12 weeks		

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Table 3. (cont.) Studies of COX-2 Selective NSAIDs in Patients with Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Rheumatoid Arthritis				
Bombardier et al., 2000	RCT	Rofecoxib 50 mg	4,047	The naproxen group reported a higher number of perforations, gastric ulcers, duodenal ulcers, and bleeding in confirmed, unconfirmed, and complicated confirmed upper GI events vs. the rofecoxib group. Bleeding episodes were more common in the naproxen group = 82 vs. the rofecoxib group = 31. More patients in the naproxen group withdrew from therapy due to GI-related ADRs (10.6% vs. 7.8%). The incidence of myocardial infarctions was higher in the rofecoxib group = 0.4% vs. the naproxen 0.1%.
		Naproxen 1,000 mg Treatment = until clinical upper GI event was seen (median follow-up was 1 months)	4,029	
Emery et al., 1999	RCT	Celecoxib 400 mg	326	Celecoxib and diclofenac were equally efficacious in the global assessments, painful/tender joints, and swollen joints outcome measures. Significantly more injury (erosion +/- ulcer) to the gastric and duodenal mucosa was seen in diclofenac vs. celecoxib. More patients withdrew due to ADRs and more GI ADRs, increases in liver function tests, decreases in hemoglobin were seen with diclofenac. Five patients receiving diclofenac required hospitalization.
		Diclofenac 150 mg Treatment = 24 weeks	329	
Schnitzer et al., 1999	RCT	Placebo	168	Significant improvement in ACR 20 response, patient/investigator global assessment of pain/disease, HAQ for rofecoxib 25 and 50 mg vs. placebo. The incidence of ADRs was similar in each group. PUBs were not reported.
		Rofecoxib 5 mg	158	
		Rofecoxib 25 mg	171	
		Rofecoxib 50 mg Treatment = 8 weeks	161	

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Table 3. (cont.) Studies of COX-2 Selective NSAIDs in Patients with Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Rheumatoid Arthritis				
Simon et al., 1999	RCT	Placebo	231	Overall, the celecoxib groups showed similar efficacy to naproxen and were superior to placebo in the global assessments, improvement in pain, tender/painful joints, improvement in ACR criteria, AM stiffness, and HAQ. The naproxen group had a higher incidence of gastroduodenal ulcers (26%) vs. the celecoxib and placebo groups (4%–6%).
		Celecoxib 200 mg	240	
		Celecoxib 400 mg	235	
		Celecoxib 800 mg	218	
		Naproxen 1,000 mg	225	
		Treatment = 12 weeks		
		Osteoarthritis or Rheumatoid Arthritis		
Silverstein et al., 2000	RCT	Celecoxib group	Celecoxib group	The annualized incidence of upper GI ulcers was lower with the celecoxib (0.76%, 11 events/1,441 patient-years) vs. the NSAID group (1.45%, 20 events/1,384 patient-years), although this difference was not statistically significant. A significant difference was seen for the annualized incidence of upper GI ulcers with symptomatic gastroduodenal ulcers when celecoxib was compared to NSAIDs (2.08%, 30 events/1,441 patient-years vs. 3.54%, 49 events/1,384 patient-years) ($p = .02$). In the celecoxib group, low-dose aspirin users had a significantly higher incidence of GI ulcer complication (0.72%, 6 events/833 patients) vs. non-aspirin users (0.16%, 5 events/3,154 patients; $p = .01$).
		Celecoxib 400 mg	3,987	
		NSAID group	NSAID group	
		Ibuprofen 2400 mg	1,985	
		Diclofenac 150 mg	1,996	
		Treatment = 6 months		

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Table 3. (cont.) Studies of COX-2 Selective NSAIDs in Patients with Arthritis*				
Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis or Rheumatoid Arthritis				
Simon et al., 1998	RCT	RA	RA	RA
		Placebo	85	All groups (except the celecoxib 80 mg) showed significant improvement from baseline values and vs. placebo in the global assessments, painful/tender joints, improvement in ACR modified criteria. More patients withdrew in the placebo group (18%) than the celecoxib 200 and 400 groups (4% and 5%).
		Celecoxib 80 mg	81	
		Celecoxib 400 mg	82	
		Celecoxib 800 mg	82	
		Treatment = 4 weeks		
		OA	OA	OA
		Placebo	71	All doses of celecoxib showed a significant improvement from baseline values and vs. placebo in the patient assessment of pain and global assessment. ADRs reported were similar among all groups.
		Celecoxib 80 mg	73	

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Table 3. (cont.) Studies of COX-2 Selective NSAIDs in Patients with Arthritis*				
Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis or Rheumatoid Arthritis				
		Celecoxib 400 mg	76	
		Celecoxib 800 mg	73	
		Treatment = 4 weeks		
		Safety	Safety	Safety
		Placebo	32	Significantly more erosions or ulcers were seen with naproxen vs. celecoxib.
		Celecoxib 200 mg	32	No effects on platelets were seen with the celecoxib group.
		Celecoxib 400 mg	32	
		Naproxen 1,000 mg	32	
		Treatment = 7 days		
<p>*Summarized from a review commissioned by the American Pain Society and conducted by Linda Tylec, PharmD, Anthony Dalpiaz, PharmD, Drug Information Service, University Hospitals and Clinics, University of Utah Health Sciences Center, 2001. Key: ADRs = adverse drug reactions; GI = gastrointestinal; HAQ = Stanford Health Assessment Questionnaire Disability Index; NSAID = nonsteroidal antiinflammatory drug; PUBs = upper GI perforations, symptomatic gastroduodenal ulcers, and upper GI tract bleeding; RCT = randomized controlled trials</p>				

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Table 4. Studies of Opioids in Patients with Osteoarthritis and Rheumatoid Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Bird, Hill, Stratford, Ferrin, & Wright, 1995	RCT Double-blind Crossover	Tramadol 50 mg 4/d	30	No clinical or statistical difference in pain relief efficacy for tramadol compared to pentazocine. For side effects, little information was found for comparisons. There was no difference in dropouts due to side effects.
		Pentazocine 50 mg 4/d	30	
Boissier et al., 1992	RCT Parallel Knee or hip OA	Paracetamol 400 mg and dextro- propoxyphene HCl 30 mg (Di-Antalvic) 6 tablets/d	70	Codeine and paracetamol vs. dextro-propoxyphene and paracetamol were not statistically different for pain relief. The dropouts due to side effects were worse with codeine (risk difference 25%). Individual side effects were not reported.
		Paracetamol 500 mg and codeine 30 mg (Efferalgan- codeine)	71	
Caldwell et al., 1999	RCT Parallel group OA Breakthrough	Controlled- release oxy- codone, 10 mg b.i.d. Placebo	34	Oxycodone controlled-release effect was clinically and statistically significant (19%–53% relative improvement over placebo). Side effects are more common than placebo. Dropouts due to adverse effects more common than placebo. (nausea, constipation, drowsiness, dizziness) but not statistically significant. Dropouts due to adverse effects more common than for placebo (13% risk difference, $p = .02$).
			36	
		Controlled- release oxy- codone 20 mg 2/d Immediate- release oxy- codone and acetaminophen 325 mg q.i.d.	34	No difference in pain efficacy. Side effects common with oxycodone immediate release, in particular, nausea was statistically significant (28% risk difference).
			37	

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Table 4. (cont.) Studies of Opioids in Patients with Osteoarthritis and Rheumatoid Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Doak et al., 1992	RCT Double-blind Crossover 1 week OA	Codeine (amount not reported)	49	Codeine alone was not clinically or statistically better than placebo. Dropouts due to side effects were nonsignificant.
		Placebo	52	
		Ibuprofen 300 mg controlled release and normal release codeine phosphate 20 mg	51	No significant clinical benefit (i.e., greater than 15% pain relief relative to the control group). Side effects were not significant.
		Ibuprofen 300 mg controlled release	53	
Jensen & Ginsberg, 1994	RCT Double-blind Parallel	Ibuprofen and codeine	51	No clinically or statistically relevant difference between codeine and ibuprofen and codeine alone. Only nausea and dropouts due to side effects were reported, and these were not statistically significant.
		Codeine	49	
		Tramadol 100 mg 3/d	135	No clinical or statistical difference in pain relief efficacy for tramadol compared to dextropropoxyphene. Compared to propoxyphene, tramadol has a worse side effect profile.
		Dextropropoxyphene 100 mg 3/d	129	
Kjaersgaard-Anderson et al., 1990	RCT Parallel OA Hip	Codeine 60 mg and paracetamol 1,000 mg 3/d	83	The effect of codeine and paracetamol vs. paracetamol were not clinically or statistically significant. Dropouts due to side effects were clinically significant (26% greater than analgesic alone).
		Paracetamol 1,000 mg 3/d	75	

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Table 4. (cont.) Studies of Opioids in Patients with Osteoarthritis and Rheumatoid Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Lloyd, Costello, Eves, James, & Miller, 1992	RCT Double-blind Crossover Severe OA of hip	Dihydrocodeine controlled-release 60 mg 1-2 tablets, 2/d	27	Codeine alone was less beneficial for pain relief compared to dextropropoxyphene and paracetamol, and this difference was equal to 11.9 mm on 100 mm pain scale. This difference was statistically significant. Side effect profile was worse in the codeine treatment arm.
		Dextropropoxyphene 325 mg paracetamol 325 mg-2 tablets 3/d	35	
Peloso, 2000	RCT Parallel OA Hip or knee	Codeine (controlled release) 100 mg/d dose escalated to 400 mg/d after 4 weeks and acetaminophen 650 mg	31	Clinical and statistical benefit of codeine 400 mg/day and acetaminophen 650 mg compared to acetaminophen alone.
		Placebo and acetaminophen 650 mg	35	
Quiding et al, 1992	RCT Crossover 24 hr Hip OA awaiting surgery	Ibuprofen and codeine 20-30 mg q 4 hr	26	Statistically significant improvement in pain relief of codeine and ibuprofen compared to placebo. Side effects were not significantly different from placebo, although nausea was 15% greater in the codeine and ibuprofen than the placebo group.
		Ibuprofen 200 mg	26	
		Placebo	26	

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Table 4. (cont.) Studies of Opioids in Patients with Osteoarthritis and Rheumatoid Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Osteoarthritis				
Roth, et al., 2000	RCT Parallel group OA 14 days	Controlled-release oxycodone 20 mg 2/d	44	Oxycodone 20 mg had greater efficacy for pain relief than oxycodone 10 mg. The dropout rate due to side effects and occurrence of nausea, constipation, and drowsiness were increased relative to oxycodone 10 mg or placebo.
		Oxycodone controlled-release 10 mg 2/d	44	
		Placebo	45	
Saltzman & Brobyn, 1983	RCT Parallel OA pain	Suprofen 200 mg 4/d	24	No difference in pain relief between propoxyphene and suprofen in these two trials. Side effects were not reported in either trial.
		Propoxyphene 65 mg 4/d	25	
		Suprofen 200 mg 4/d	24	
		Propoxyphene 65 mg 4/d	26	
Rheumatoid Arthritis				
Bourreau, Delacoeuille, & Orvain, 1990	RCT Double-blind Parallel RA with persisting pain	Codeine 30 mg and paracetamol 500 mg 3/d	9	Codeine showed some benefit over placebo for pain relief but no statistical difference calculated.
		Placebo	5	
		Codeine 30 mg and paracetamol 500 mg 3/d	20	
Hardin, Jr. & Kirk, 1979	CCT Crossover Definite RA-ARA inpatients	Codeine Sulfate 65 mg	17	Results showed some benefit of codeine over placebo in pain relief but there was not significant statistical difference calculated. Side effects profile not reported. Constipation was only statistically significant side effect noted between codeine and placebo.
		Placebo	14	

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Table 4. (cont.) Studies of Opioids in Patients with Osteoarthritis and Rheumatoid Arthritis*				
Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Rheumatoid Arthritis				
Ingpen, 1969	RCT Crossover RA (ARA)	Codeine sulfate 65 mg	17	Codeine not clinically different than pentazocine. Side effects were common—almost 1/2 of patients in both groups reported some sort of side effect.
		Pentazocine HCl 50 mg	16	
		Codeine sulfate 65 mg	17	Codeine provides clinically relevant pain relief of 20% relative to propoxyphene. This difference was not statistically significant ($p = 0.13$) side effects were common in both groups (> 30% of patients), occurred more frequently with codeine than propoxyphene (17% risk difference) but this was not statistically significant.
		Propoxyphene HCl 50 mg	11	
		Codeine Sulfate 65 mg	17	Codeine was better than ASA for pain relief but this difference was not clinically relevant (only 10% relative difference) nor was it statistically significant. Side effects were common in both groups (> 25% of patients).
		Aspirin 650 mg	20	
		Pentazocine HCl 50 mg	16	No significant difference in side effects profiles of pentazocine over active comparators.
		Propoxyphene HCl 50 mg	11	
		Pentazocine HCl 50 mg	16	No usable efficacy data
		Aspirin 650 mg	20	
		Dextropropoxyphene 150 mg Indomethacin 25 mg		

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Table 4. (cont.) Studies of Opioids in Patients with Osteoarthritis and Rheumatoid Arthritis*

Author(s)	Study Design	Intervention (daily dose)	Number of Patients	Results
Rheumatoid Arthritis				
Nuki et al., 1973	RCT Crossover RA (ARA)	Pentazocine (Fortral) 25 mg q 4 h	4	Pentazocine did not show improvement in pain relief compared to placebo. There were no statistically significant differences in the side effect profiles of pentazocine over placebo.
		Placebo	13	
Osteoarthritis and Rheumatoid Arthritis				
Brooks, Dougan, Mugford, & Meffin, 1982	RCT Crossover OA and RA Single dose	Dextropropoxyphene 65 mg	24	Propoxyphene was 7% better than placebo for pain relief after a single dose but this difference was not statistically significant.
		Placebo	24	
		Dextropropoxyphene HCl 65 mg and paracetamol 650 mg	24	Propoxyphene and analgesic was not statistically or clinically different from analgesic alone. Side effects were not reported.
		Paracetamol 650 mg	24	
Mitchell, Cunningham, Mathews, & Muir, 1984	CCT Crossover RA or OA who required analgesia	Dextropropoxyphene 65 mg	43	This trial showed a benefit of propoxyphene of 0.78, but the units of improvement were not reported. The trial reported no statistical significance ($p = .07$). Side effects were unavailable.
		Placebo	41	
		Dextropropoxyphene 65 mg and paracetamol 650 mg (DIG)	44	Results show improvement in pain relief with propoxyphene and paracetamol vs. paracetamol alone ($p = .07$).
		Paracetamol 650 mg	44	

*Summarized from a review commissioned by the American Pain Society and conducted by Husni, M.E., Simon, L., Welch, V., Shea, B., Peterson, J., Tugwell, P., Wells, G. Opioids for Rheumatoid Arthritis and Osteoarthritis: A Cochrane Review. Harvard Medical School, Beth Israel Deaconess Medical Center and Institute for Population Health, University of Ottawa. Report to the American Pain Society, February, 2001.

Key: RCT=randomized controlled trial, OA=osteoarthritis, RA=rheumatoid arthritis, CCT=controlled clinical trial, ARA=adult rheumatoid arthritis

*Summarized from a review commissioned by the American Pain Society and conducted by Husni, M.E., Simon, L., Welch, V., Shea, B., Peterson, J., Tugwell, P., Wells, G. Opioids for Rheumatoid Arthritis and Osteoarthritis: A Cochrane Review. Harvard Medical School, Beth Israel Deaconess Medical Center and Institute for Population Health, University of Ottawa. Report to the American Pain Society, February, 2001.

Key: RCT=randomized controlled trial, OA=osteoarthritis, RA=rheumatoid arthritis, CCT=controlled clinical trial, ARA=adult rheumatoid arthritis

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Classification of Evidence

The evidence was classified by type and strength. The type of evidence for recommendations was ranked ordinally in categories from I to V. The following summarizes the types of evidence that support interventions discussed in the guideline:

- I. Meta-analysis of multiple well-designed controlled studies
- II. Well-designed experimental studies
- III. Well-designed quasi-experimental studies such as nonrandomized controlled, single-group pre-post, cohort, time series, or matched-case controlled studies
- IV. Well-designed nonexperimental studies such as comparative and correlational descriptive and case studies
- V. Case reports and clinical examples

The strength and consistency of evidence for the recommendations summarize the evidence and note whether the evidence was generally consistent or inconsistent. Strength of evidence ranges from A, which is the strongest evidence, to D, which indicates that there is little or no evidence, or that only type V evidence exists. The strength and consistency of the recommendations are as follows:

- A. There is evidence of type I or consistent findings from multiple studies of types II, III, or IV.
- B. There is evidence of types II, III, or IV, and findings are generally consistent.
- C. There is evidence of types II, III, or IV, but findings are inconsistent.
- D. There is little or no evidence, or there is type V evidence only.

Panel consensus: Practice recommended based on the opinions of experts in pain management.

When the strength of evidence was A or B, the panel's recommendations were based primarily on the evidence. When the strength of recommendation was C or D, the panel used the available empirical evidence, but based its recommendations primarily on expert judgment. The term "Panel consensus" was used when the recommendation was a statement of panel opinion regarding desirable practice. Table 6 summarizes the scientific evidence for the management of pain in adult populations. Table 7 lists published systematic evidence reviews in children and adolescents. Table 8 summarizes the scientific evidence for pain management in children and adolescents.

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Table 5. APS-Conducted Systematic Evidence Reviews on Pain Management in Adults

- Orthotic devices for pain relief in OA and RA; knee braces, foot orthoses, wrist braces, and compression gloves
- Surgical interventions for pain relief in OA and RA: arthroplasty, arthrodesis, and arthroscopy
- Transcutaneous electrical nerve stimulation (TENS) for pain relief in OA and RA
- Exercise and physical training for pain relief in OA and RA
- Pulsed electromagnetic field therapy for pain relief in OA and RA
- Cognitive-behavioral therapy for pain relief in OA and RA

Table 6. Scientific Evidence for Pain Reduction in Adults

Intervention	Source of Evidence	Type of Evidence	Strength and Consistency of Evidence
Analgesics			
Acetaminophen	D	II	A
NSAIDs—nonselective	C, O	I, II	B, C ^a
NSAIDs—COX-2 selective	A	II	B
Topical agents	D	II, III, IV	C
Intra-articular glucocorticosteroids	C	II	B
Hyaluronic acid	C, A	II	B
Opoids	O	II, III, IV	B
Tramadol	C	I	C
Disease-modifying antirheumatic drugs	C	II	B, C
Dietary Supplements			
Glucosamine sulfate	C, O	I, II	A
Chondroitin 4-sulfate	O	II	C
S-adenosylmethionine	O	I, II	C
Physical Modalities			
TENS	AP, C	II	C
Acupuncture	O	I, II	C
Magnets	AP	II, III	C
Orthotics	AP	II, III	B, C ^a
Surgery	AP	II, III, IV	B, C ^a
Patient Education	AP, O	II, III	B
Cognitive-Behavioral	AP	II	B

^a Depends on medication, orthotic device, or surgical procedure studied

Key:

Source of Evidence

C = Cochrane collaboration review; O = Other published review; A = APS commissioned review; AP = APS panel/staff review

Type of evidence

I = Meta-analysis of multiple well-designed controlled studies; II = Well-designed experimental studies; III = Well-designed quasi-experimental studies such as nonrandomized controlled, single-group pre-post, cohort, time series, or matched-case control studies; IV = Well-designed nonexperimental studies such as comparative and correlational descriptive and case studies; V = Case reports and clinical examples

Strength and consistency of evidence

A = Evidence of type I or consistent findings from multiple studies of types II, III, or IV; B = Evidence of types II, III, IV, and findings are generally consistent; C = Evidence of types II, III, IV, but findings are inconsistent; D = Little or no evidence, or there is type V evidence only

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Table 7. Published Systematic Evidence Reviews on Pain Management in Juvenile Chronic Arthritis

Cochrane Collaboration Reviews	
Disease-modifying antirheumatic drugs	Takken, T., Van der Net, J., & Henders, P.J.M. (2001). Methotrexate for treating juvenile idiopathic arthritis <i>Cochrane Database Systematic Review</i> , (3), CD003129.
Nutrition	Poustie, V.J., Snyth, R.L., & Watling, R.M. (2000). Oral protein calorie supplementation for children with chronic disease. <i>Cochrane Database Systematic Review</i> , (3), CD001460.
Other Published Systematic Reviews	
Other	ter Riet, G., de Graen, A.J., de Boer, A., & Kessels, A.G. (1998). Is placebo analgesia mediated by endogenous opioids? A systematic review. <i>Pain</i> , 76(3), 273–275.

Table 8. Scientific Evidence for Pain Reduction in Children

Intervention	Source of Evidence	Type of Evidence	Strength and Consistency of Evidence
Analgesics			
Nonsteroidal antiinflammatory drugs—nonselective	AP	II, III	B
Intra-articular glucocorticosteroids		II, III	B, C
Disease-Modifying Antirheumatic Drugs	AP	II	C
Surgery	AP	IV	B
Cognitive-Behavioral	AP	III	C

Key:**Source of Evidence**

C = Cochrane collaboration review; O = Other published review; A = APS commissioned review; AP = APS panel/staff review

Type of evidence

I = Meta-analysis of multiple well-designed controlled studies; II = Well-designed experimental studies; III = Well-designed quasi-experimental studies such as nonrandomized controlled, single-group pre-post, cohort, time series, or matched-case controlled studies; IV = Well-designed nonexperimental studies such as comparative and correlational descriptive and case studies; V = Case reports and clinical examples

Strength and consistency of evidence

A = Evidence of type I or consistent findings from multiple studies of types II, III, or IV; B = Evidence of types II, III, IV, and findings are generally consistent; C = Evidence of types II, III, IV, but findings are inconsistent; D = Little or no evidence, or there is type V evidence only

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III. Pain Assessment

Recommendations in This Section*

1. Treatment of people with arthritis should include, in addition to a complete history and physical examination, an initial comprehensive pain assessment and ongoing assessment of pain and functional status to identify, implement, and evaluate effectiveness of pain interventions. Pain assessment should focus on the type and quality of pain, source, intensity, location, duration/time course, pain affect, and effects on personal lifestyle. (Panel consensus)
2. Self-report should be the primary source of pain assessment when possible. Behavioral observations and physiologic measurements may provide additional information but should not be used as the primary source of pain assessment. Exceptions are preverbal children and nonverbal and cognitively impaired individuals, for whom behavioral observation should be the primary source for pain assessment. (B)
3. Selection of an appropriate pain assessment tool should take into consideration the person's cognitive development, language, culture, and preferences. Use the same pain assessment tool for the person on subsequent assessments to facilitate reliable evaluations of changes in the pain. (B)
4. Because pain is a major cause of disability in people with arthritis, assessment of functional status should be included in the pain assessment. When selecting a functional status measure, consideration should be given to the cognitive-developmental abilities of the person, the type of practice setting, the domains of function to be assessed, and the time and resources needed to complete the assessment. (B)
5. When arthritis pain is persistent or severe, the clinician should conduct a comprehensive assessment, including an evaluation of biological, psychological, or social factors that may be contributing to pain as well as an assessment of the overall impact of pain on function. (Panel consensus)

*Please note: Recommendations appear in bold type as they are discussed in the text. See Chapter II for an explanation of the strength of the evidence supporting the recommendations.

Types and Sources of Pain

Arthritis pain is a complex experience that is influenced not only by biological factors such as disease severity but also by psychosocial factors. Treatment of people with arthritis should include, in addition to a complete history and physical examination, an initial comprehensive pain assessment and ongoing assessment of pain and functional status to identify, implement, and evaluate effectiveness of pain interventions. Pain assessment should focus on the type

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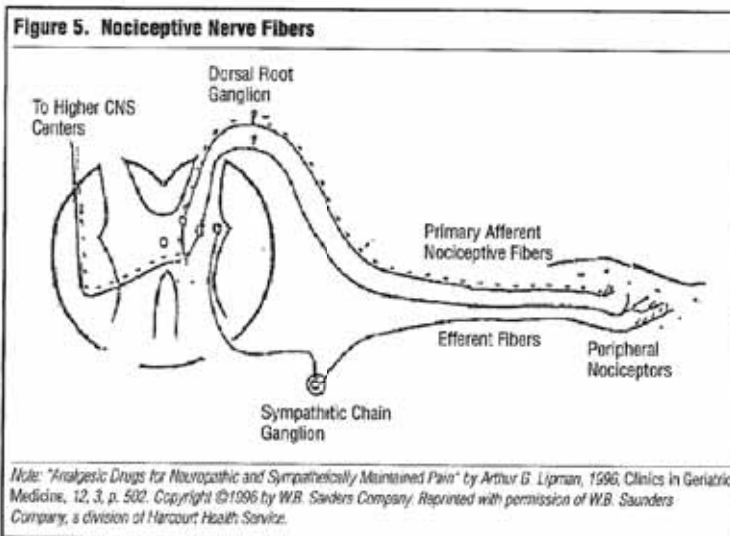
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and quality of pain, source, intensity, location, duration/time course, pain affect, and effects on personal lifestyle.

The goals of pain assessment are to describe the pain and to provide a comprehensive assessment of biological, psychological, and social factors that influence the pain and that can be used to guide treatment. Accurate pain assessment requires differentiation by type and course of pain. Two types of pain are nociceptive and neuropathic. Nociceptive pain results from actual or potential tissue damage. The pain results from ongoing activation of primary afferent nociceptive neurons by noxious stimuli in an intact nervous system. Neuropathic pain results from a disturbance of function or pathologic change in a nerve. Correct assessment of the type of pain is necessary for determining appropriate pain treatment.

Most osteoarthritis (OA) and rheumatoid arthritis (RA) pain is nociceptive. Transduction of noxious stimuli that result in nociceptive pain occurs at peripheral nociceptors, the lightly myelinated nerve endings at the distal ends of primary afferent nociceptive nerve fibers (Figure 5). Prostaglandins are important mediators of pain and inflammatory stimuli at nociceptors. Nonsteroidal antiinflammatory drugs (NSAIDs) act at these sites. Transmission of the impulses that produce nociceptive pain proceeds from the peripheral site of the stimulus to the spinal cord, where opioids act to decrease pain perception.



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Neuropathic pain may be either peripheral or central. Peripheral neuropathic pain results from direct damage to a nociceptive neuron and not to stimulation of the nociceptors. Central neuropathic pain results from damage to an afferent neuron within the central nervous system. Because neuropathic stimuli occur proximally to the nociceptors, NSAIDs (that work primarily at the nociceptors) are not effective analgesics for neuropathic pain. Causes of peripheral neuropathic pain in OA and RA include physical damage to the neurons from malalignment of joints, trauma from falls, and surgery. Some patients with OA or RA, or both, develop neuropathic pain from postherpetic neuralgia, diabetic neuropathy, or nerve trauma. Management of nociceptive and neuropathic pain is discussed in Chapter IV.

Pain from musculoskeletal sources may arise from stimulation of nociceptors by inflammatory products and neurochemicals such as prostaglandins and bradykinins as well as from stimulation of mechanoreceptors. The pain stimulus may arise directly from a primary site, be mediated by peripheral or central sensitization arising from previous painful episodes, or both. The clinical consequence of sensitization is increased pain in response to a noxious stimulus (hyperalgesia) or pain in response to an innocuous stimulus (allodynia) so that normal kinesthetic messages of pressure or joint motion received by mechanoreceptors now are interpreted as pain. Musculoskeletal pain in arthritis may be related to the disease process, may be activity-induced, or may be related to inactivity and deconditioning. Table 9 presents sources of musculoskeletal pain in arthritis.

Assessment details specific to surgical interventions and to pain in children are presented in those respective sections of the guideline.

Pain Measures

Self-report should be the primary source of pain assessment when possible. Behavioral observations and physiologic measurements may provide additional information but should not be used as the primary source of pain assessment. Exceptions are preverbal children and nonverbal and cognitively impaired individuals, for whom behavioral observation should be the primary source for pain assessment.

Pain Intensity

The three most common methods for assessing pain intensity in adults are (a) numeric rating scales, (b) visual analog scales, and (c) verbal rating scales. Examples of the first two methods are presented in Figure 6. On a numeric rating scale, the person is asked to select a number (e.g., from 0 = no pain to 10 = pain as bad as it can be) that best describes the intensity of the pain. A visual analog scale usually consists of a 10-cm line with descriptors at the endpoints (e.g., no pain to the worst pain imaginable). The person places a mark along the line to

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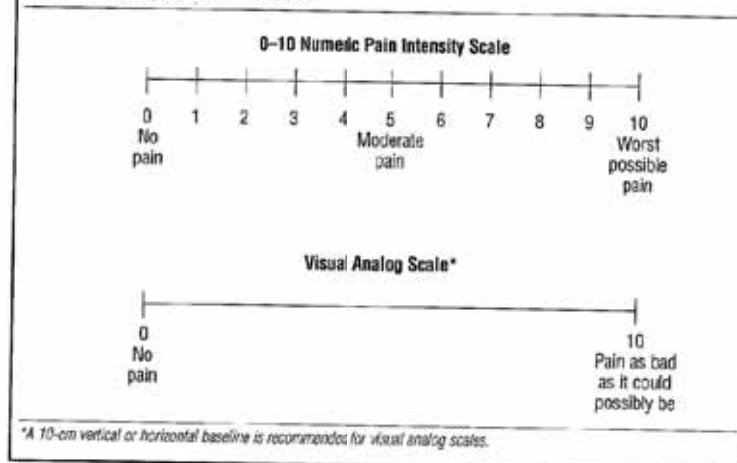
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Table 9. Sources of Musculoskeletal Pain in Arthritis

Location	Disease-Related	Activity-Related	Inactivity-Related
Joint: Capsule, Synovium, Ligaments	Inflammatory mediators; substance P; swelling/ intra-articular pressure	Sprains/strains; pathologic impact; increased intra-articular pressure by muscle co-contraction or sustained joint flexion	Decreased elasticity; decreased compliance of soft tissues; decreased shock attenuation
Bone and Periosteum	Periosteal pressure; osteophytes; maldistribution of impact forces from bony malalignment; cartilage disruption	Stress fractures	Osteoporotic fracture; postural/bony malalignment
Muscle and Tendon	Inflammatory products; muscle tenderness, spasm; vascular compression; dysfacilitation	Postexertional muscle soreness; overstretched soft tissues; repetitive trauma; epinephrine; hyperalgesia/allodynia	Muscle de-conditioning (weakness, atrophy, fatigue); increased risk of injury; decreased shock attenuation by neuromuscular mechanisms; lowered pain threshold

Figure 6. Examples of Pain Scales

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indicate the intensity of pain, and a pain intensity score is determined by measuring the distance from the 0 point to the mark. A verbal rating scale consists of a series of pain descriptors usually arranged in order from the lowest level of pain to the highest. The person selects the descriptor that best characterizes the pain intensity. Numerous studies have provided support for the reliability and validity of pain intensity measures. (See Jensen & Karoly, 1992, for a review of this literature.) These measures are easy to use, sensitive enough to detect changes in pain that occur following pain treatment, and can be used repeatedly over the course of treatment to monitor progress.

Having patients rate the intensity of current pain, as well as the worst pain, least pain, and average pain the person has experienced in the past week, is useful in assessing variations in pain.

Pain Affect

A second important dimension of the pain experience is pain affect, which is the unpleasantness and emotional arousal caused by pain. Pain affect and pain intensity represent distinct dimensions of pain but are related, with patients who have higher levels of pain intensity reporting more affectively unpleasant pain (Jensen, Karoly, O'Riordan, Bland, & Burns, 1989). Some medications for pain are effective primarily because they reduce the affective unpleasantness of pain, whereas others are effective because they reduce pain intensity. Some nonpharmacologic interventions such as hypnosis and imagery exert their effects primarily through reducing the affective unpleasantness of pain rather than by changing pain intensity.

Pain affect and pain intensity can be measured at the same time. The two most common measures of pain affect are visual analog and verbal descriptor scales. An example of a visual analog scale for assessing pain affect is a 10-cm line whose endpoints are labeled *not at all unpleasant* and *most unpleasant pain imaginable*. A verbal descriptor scale for assessing pain affect could include descriptors such as *bearable*, *unpleasant*, *distressing*, *miserable*, *dreadful*, *agonizing*, and *excruciating*.

Pain Location

Pain location is most easily assessed by using a body map, which consists of an outline of a human figure (or body region) on which the person is asked to shade in the areas where they are experiencing pain. Body maps are scored by using templates that provide an index of the number of body areas or the percentage of body area affected. Body maps are easy to use and provide a rapid method of assessing changes in pain location. (See Figure 7.) These measures are particularly useful when multiple pain sites are present and when changes in the overall body area affected by pain might be expected to provide an index of improvement. It may be easier for the cognitively impaired person to point to the pain sites on their bodies rather than to use a drawing.

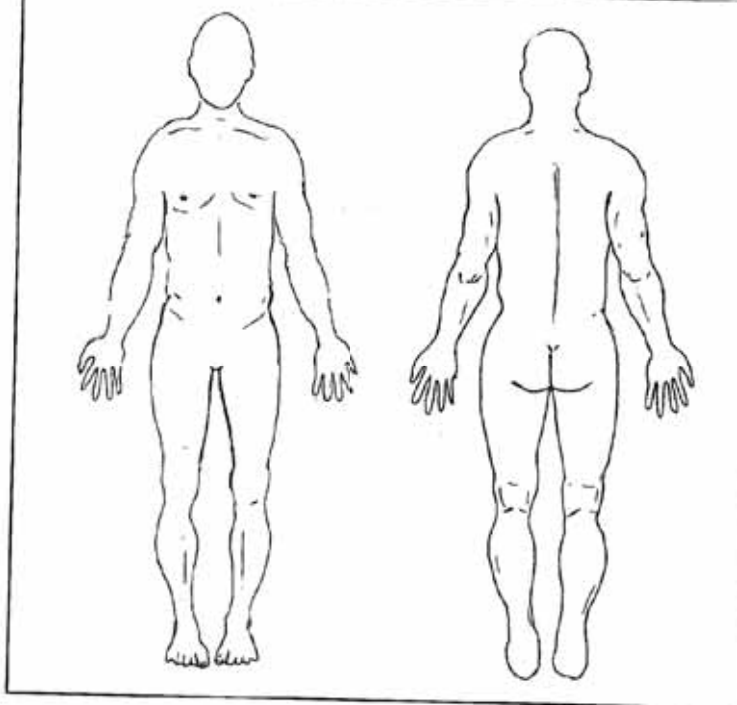
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Figure 7. Example of Body Map for Location of Pain



Pain Duration and Time Course

People with arthritis should be asked routinely about the duration of daily pain and about the time course of their pain. Interviews on daily diary records in which people report on their pain multiple times each day (e.g., morning, noon, evening, bedtime) can provide insights into variations in the duration and time course of pain.

Selection of Standardized Pain Measures

Selection of an appropriate pain assessment tool should take into consideration the person's cognitive development, language, culture, and preferences. Use the same pain assessment tool for the person on subsequent assessments to facilitate reliable evaluations of changes in the pain.

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Tables 31 and 32 in Appendix A describe pain measures appropriate for various ages.

Impact of Pain on Function

Pain can have a major impact on a person's ability to engage in daily activities and to maintain a functionally independent lifestyle. Because pain is a major cause of disability in people with arthritis, assessment of functional status should be included in the pain assessment. When selecting a functional status measure, consideration should be given to the cognitive-developmental abilities of the person, the type of practice setting, the domains of function to be assessed, and the time and resources needed to complete the assessment.

Health status measures can be used to assess the impact of pain on function. Two measures well suited for this purpose are the Health Assessment Questionnaire (HAQ; Ramey, Raynauld, & Fries, 1992) and Arthritis Impact Measurement Scales (AIMS; Meenan, Mason, Anderson, Guccione, & Kazis, 1992). HAQ and AIMS are standardized, reliable measures. There are short versions of both the HAQ (Pincus, Summey, Soraci, Wallston, & Hummon, 1983) and the AIMS (Lorish, Abraham, Austin, Bradley, & Alarcon, 1991). The American College of Rheumatology's classification of functional status in RA, presented in Table 10, is another commonly used measure of functioning. The Functional Interference Estimate is a useful measure to determine how much pain interferes with a person's functioning (Toomey, Mann, Hernandez, & Abashian, 1993). Other instruments to measure various aspects of functioning are presented in Appendix B, Tables 34 and 35.

Table 10. American College of Rheumatology's Classification of Functional Status in Rheumatoid Arthritis

Class	Definition*
I	Completely able to perform usual activities of daily living (self-care, vocational, and avocational)
II	Able to perform usual self-care and vocational activities, but limited in avocational activities
III	Able to perform usual self-care activities, but limited in vocational and avocational activities
IV	Limited in ability to perform usual self-care, vocational, and avocational activities

*Usual self-care activities include dressing, feeding, bathing, grooming, and toileting. Avocational (recreational and/or leisure) and vocational (work, school, homemaking) activities are patient-desired and age- and sex-specific.

Note. From "The American College of Rheumatology 1991 Revised Criteria for the Classification of Global Functional Status in Rheumatoid Arthritis," by M.G. Hochberg, Chang, R.W., Divo, I., Lindsey, S., Pincus, T., & Wolfe, F. (1992). *Arthritis and Rheumatism*, 35(5), p. 498. Copyright 1992 by Wiley-Liss, Inc. Adapted with permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

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Comprehensive Assessment of Pain

When arthritis pain is persistent or severe, the clinician should conduct a comprehensive assessment, including an evaluation of biological, psychological, or social factors that may be contributing to pain as well as an assessment of the overall impact of pain on function.

Biological Factors

A complete medical history and physical examination should be performed to understand underlying biological factors that are contributing to persistent or severe pain. Attention should be given both to the underlying arthritis disease activity and to the presence of coexisting diseases or conditions that produce pain. The assessment should include a review of current and past treatments for pain and the effectiveness of these treatments.

Inquiry should be made regarding physical activities and exercise that may play a role in pain episodes. Types and patterns of physical stress required by work, home, and recreational demands can contribute to the pain experience. Situations such as repetitive motions, poor posture, poor body mechanics, fatigue, or excessive demands on strength or flexibility that occur episodically can result in increases in pain directly related to the activity and only indirectly to the disease itself. Furthermore, inactivity, which results in musculoskeletal deconditioning, is associated with increased joint stress and pain following even low to moderate levels of physical exertion. It is not uncommon that a painful flare-up is activity related and not an increase in disease activity.

Psychological Factors

Psychological factors known to be related to arthritis pain include pain coping strategies, self-efficacy, and helplessness (Keefe & Bonk, 1999).

Pain coping strategies include cognitive and behavioral efforts that people make to cope with their pain and disease. Coping strategies include resting, distracting oneself from pain, and using imagery or relaxation strategies. People who are able to use their pain coping strategies to control and decrease pain and who avoid overly negative thinking (catastrophizing) when experiencing pain have much lower levels of pain and disability. The instrument most commonly used to assess pain coping strategies in people with arthritis is the Coping Strategies Questionnaire, a self-report measure that provides an index of the frequency of coping efforts and the perceived effectiveness of these strategies in controlling and decreasing pain (Rosenstiel & Keefe, 1983).

Self-efficacy refers to the sense of confidence that one can accomplish a given goal such as realizing pain relief or remaining active. People with arthritis vary substantially in their sense of self-efficacy, and those high in self-efficacy for arthritis pain have been found to be more active, to be less psychologically distressed, and to have lower levels of pain. The Arthritis Self-Efficacy Scale (Lorig,

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Chastain, Ung, Shoor, & Holman, 1989) is a well-validated measure that provides an index of self-efficacy for three domains: (a) arthritis pain, (b) function, and (c) other arthritis symptoms (e.g., fatigue, mood).

Helplessness refers to the sense that one's efforts are doomed to fail. Helplessness is a particular problem in a chronic disease such as RA in which flares in pain and disease activity occur on an unpredictable basis. When people develop a sense of helplessness, they are not only more likely to experience higher levels of pain but also to experience higher levels of depression and functional impairment. The Rheumatology Attitudes Index is a brief, reliable, and valid self-report instrument that assesses helplessness (Callahan, Brooks, & Pincus, 1988).

Social Factors

People with arthritis often rely on family, friends, coworkers, and others for physical and emotional support. Social support has been found consistently to be related to adjustment to pain in people with arthritis. People who view their social networks as supportive have lower levels of depression and physical disability and are more likely to cope actively with pain. A widely used and well-validated measure of social support in people with arthritis is the Social Support Questionnaire (Parker & Wright, 1995). A comprehensive assessment focusing on these factors when pain is persistent or severe will help the clinician, in partnership with the patient, determine the best approach to treat the pain.

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IV. Management of Pain in Osteoarthritis and Rheumatoid Arthritis

Overview

Although osteoarthritis (OA) and rheumatoid arthritis (RA) are different diseases, many treatment principles are common to both. Patient education, weight control, physical exercise, cognitive-behavioral strategies, assistive devices, and surgery are used in both conditions. Analgesics and antiinflammatory medications are used in both conditions, but disease-modifying drugs are currently available only for the treatment of RA, and glucosamine sulfate has been shown to be effective for pain management in OA.

It is clear that altering the progression of disease in RA has implications for pain control. Medications such as methotrexate, leflunomide, the tumor necrosis factor (TNF)- α inhibitors, and, less so, sulfasalazine all have important effects on the signs and symptoms of RA. All have been shown to reduce pain while at the same time decreasing the progression of damage as measured by radiograph. In general, when treating patients with RA, use of appropriate disease-modifying antirheumatic drugs (DMARDs) as soon as possible after a correct diagnosis is made is critical. It also is important to use therapies such as the cyclooxygenase-2 (COX-2) selective nonsteroidal antiinflammatory drugs (NSAIDs) or nonselective NSAIDs concomitantly to achieve adequate pain control where appropriate.

The algorithms shown in Figures 8 and 9, for managing OA and RA pain, respectively, show how treatment decisions are based on the characteristics of the pain and inflammation, and the possibility of side effects.

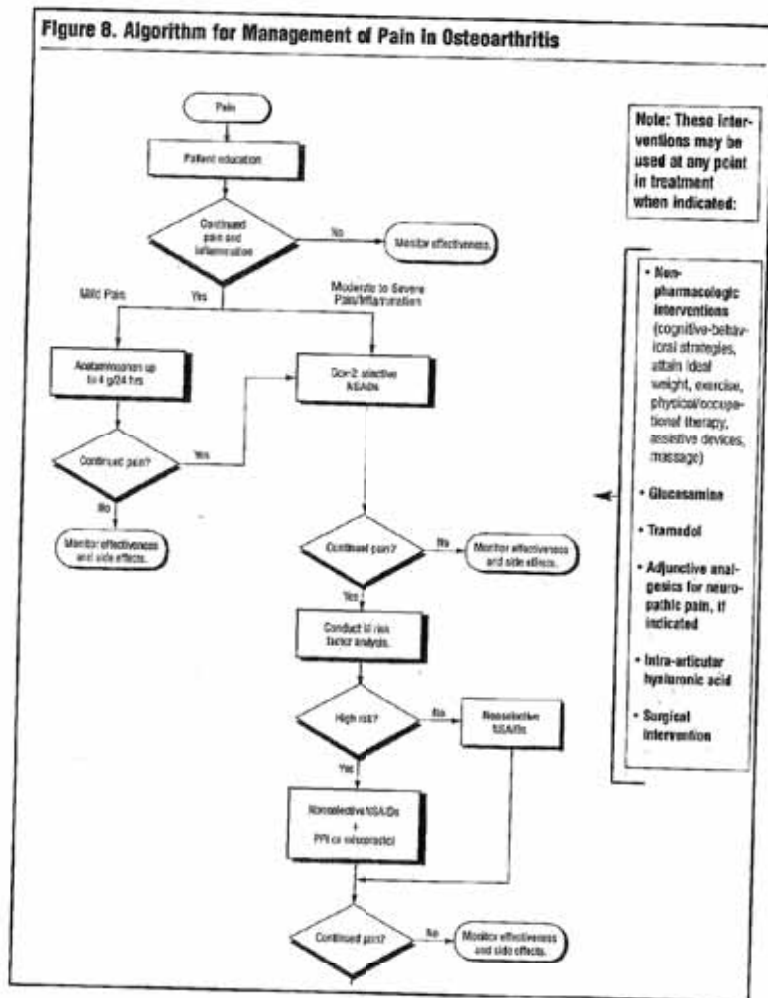
Patient education and cognitive and behavioral strategies are presented first to emphasize the importance of beginning the treatment plan with these aspects of care. This section is followed by a discussion of the use of medications, then nutrition and physical modalities including physical exercise, orthotics, and surgery. The final sections discuss the management of pain in children and older adults.

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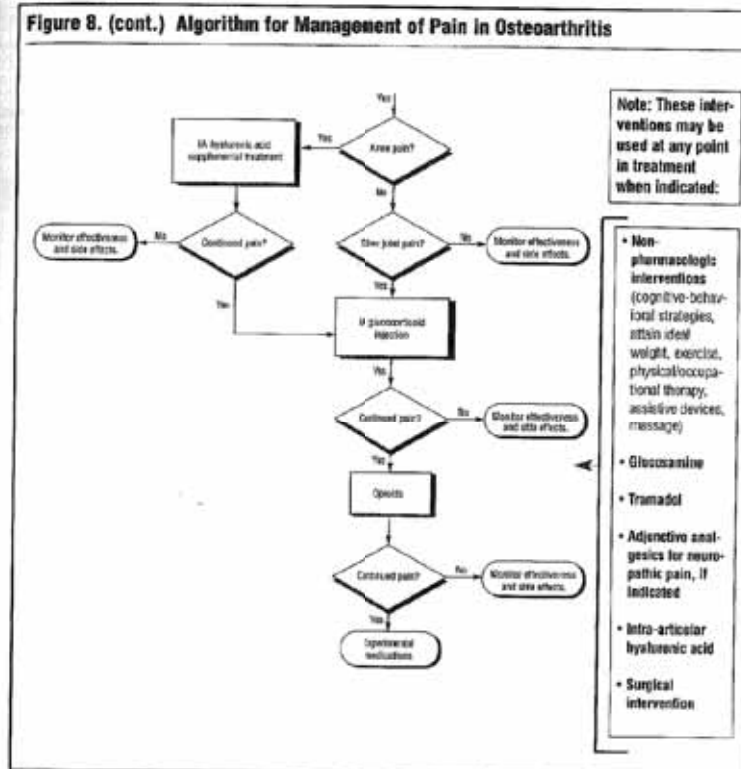
Figure 8. Algorithm for Management of Pain in Osteoarthritis

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Figure 8. (cont.) Algorithm for Management of Pain in Osteoarthritis

Patient/Family Education and Cognitive-Behavioral Interventions

Recommendations in This Section*

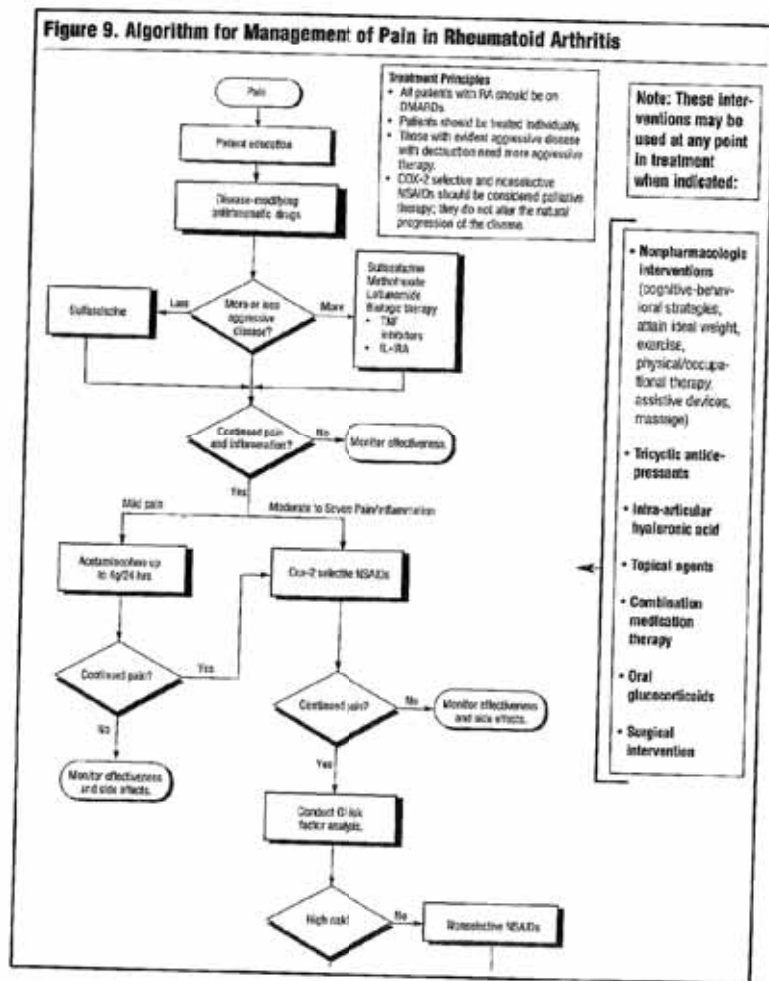
6. A patient's thoughts, feelings, emotions, and behavior, and his or her family's response, can influence the arthritis pain experience. Therefore, education about pain, pain management options, and self-management programs should be communicated to the patient and family as an integral and cost-effective part of treatment. (A)

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7. Cognitive-behavioral therapy (CBT) should be used to reduce pain and psychological disability and to enhance self-efficacy and pain coping. (B)

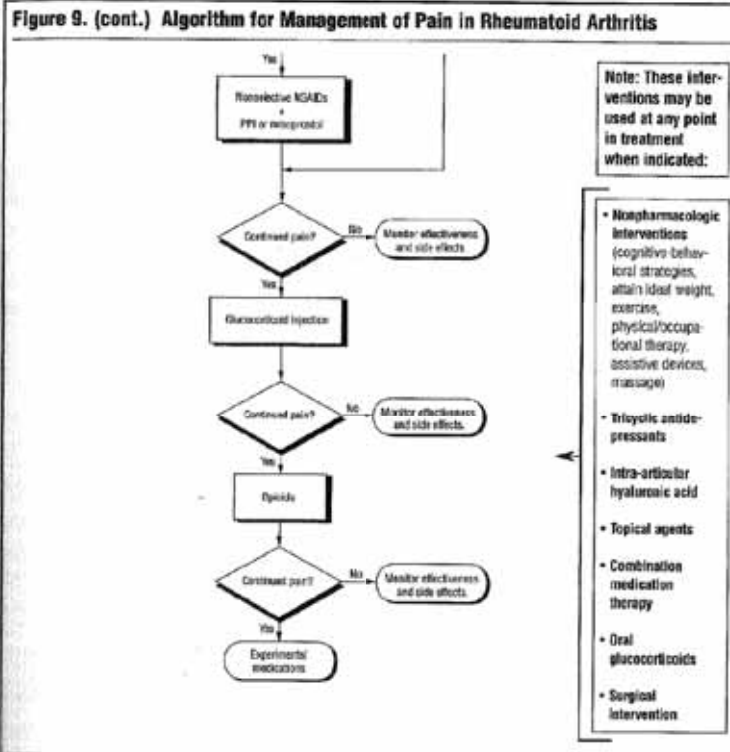
*Please note: Recommendations appear in bold type as they are discussed in the text. See Chapter II for an explanation of the strength of the evidence supporting the recommendations.

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Patient education is valuable in the treatment of people with OA, RA, or juvenile chronic arthritis (JCA). Patient education programs are comprised of a set of planned educational activities designed to improve patients' health behaviors and/or health status and to slow deterioration from disease (Lorig & Gonzalez, 1992). Programs increase patient self-confidence by focusing on teaching patients to adjust their daily activities as dictated by their disease symptoms (Hirano, Laurent, & Lorig, 1994).

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Patient Education Programs

Content. Many of the educational programs currently available are modeled after the Arthritis Self-Management Program (ASMP) developed by Lorig, Lubeck, Kraines, Seleznick, and Hoffman (1985). These programs are most commonly administered as 2-hour weekly sessions over a 6-week period. The content includes information about arthritis as a disease, medical management of arthritis, surgical procedures for arthritis pain management, rationale for self-management, goal-setting suggestions, and self-management skills such as exercise, relaxation, and energy conservation. Other types of education programs have included skill practice (Ettinger et al., 1997; Kovar et al., 1992), discussion, contracting and diaries, emotional support and/or counseling (Maisiak, Austin, & Heck, 1996). Although pain is not addressed specifically in all programs, it is measured as an outcome in the majority of programs, and content on pain and pain management can be added to programs that do not include it. The content areas for a comprehensive patient education program are as follows:

- Basic information about joint anatomy and arthritis
- Self-help principles
- Tips for using joints wisely and conserving energy
- Pain management
- Exercise
- Relaxation
- Facts about patients' medications and their effects
- Psychological aspects and problem solving
- Clinician-patient relations
- Good nutritional habits
- Methods of heat/cold application
- Identification of unproven remedies

Format. The format for patient education programs can be developed to fit the setting, budget, and resources. Numerous formats have been used successfully to present educational programs for people with arthritis. The 12-hour format (2 hours per week for 6 weeks) is the most commonly used and has been effectively presented by lay persons (Lorig, Feigenbaum, Regan, Ung, Chastain, & Holman, 1986), nurses, and other professionals (LeFort, Gray-Donald, Rowat, & Jeans, 1998; Lindroth et al., 1997) in community settings. Methods of delivering these programs vary from small group settings, which are the most frequently used, to telephone contacts, computerized programs, home study programs, and booklets, leaflets, or newsletters.

Patient education programs with varying patient types may be used. Programs have been offered for mixed groups of patients with RA and OA, or for specific groups with either form of arthritis. Some of the community-based programs also have included patients with musculoskeletal pain from other causes. Diagnoses may

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not be confirmed in these programs but often are based on patient self-report.

Outcomes. The primary outcomes of patient education programs are an increase in knowledge and an increase in self-confidence in adjusting daily activities to the disease symptoms. Short-term and often long-term decreases in pain have been seen following patient education programs (Ettinger et al., 1997; Fries, Carey, & McShane 1997; Holman, Mazonson, & Lorig, 1989; Lefort et al. 1998; Lorig, Laurin, & Holman, 1984; Maisiak et al, 1996; Weinberger, Tierney, Cowper, Katz, & Boohar, 1993). As discussed earlier, pain is a subjective phenomenon that is most reliably measured by self-report. Although the source of the pain, such as inflammatory or mechanical, may not be known, the intensity, affect, location, duration, and the effects on functional status should be measured. See Chapter II and Appendix A for information on these measures.

Improved pain ratings appear to be related to the enhancement of self-efficacy (Lorig & Gonzalez, 1992) and/or changes in learned helplessness (Goepfinger, Arthur, Baglioni, Brunk, & Brunner, 1989; Taal, Rasker, & Wiegman, 1997). Decreased pain ratings often are accompanied by an increase in function, a decrease in disability, or both. Arthritis patient education programs can lead to health behaviors such as improved nutrition, joint protection, increase in exercise, use of devices, energy conservation, and relaxation. Psychological outcomes, including depression, self-efficacy, and life satisfaction, may improve. More detailed information on cognitive-behavioral interventions, nutrition, exercise, and physical modalities is included in this chapter of the guideline.

A decrease in physician visits has been seen following patient education programs (Lorig et al., 1984). These short-term improvements have been found in patients with RA (Lorig et al., 1985) and OA (Weinberger et al., 1993).

Although there is an initial positive response to patient education programs, long-term response is variable. The initial decrease in pain intensity has been maintained at 4-month and 4-year intervals (Lorig et al., 1985), and at 1- and 5-year intervals (Lindroth, Bauman, Brooks, & Priestley, 1995). Slight increase in pain intensity over time may reflect disease progression.

Cost. Arthritis patient education programs such as the ASMP are cost-effective. Taking into account the 20% reduction in pain and the 40% reduction in physician visits seen by Lorig and colleagues following the ASMP, costs were analyzed and the ASMP was determined to be a cost-effective program for patients and healthcare providers (Lorig, Mazonson, & Holman, 1993). This conclusion was supported by other analyses in similar studies (Kruger et al., 1998). A patient's thoughts, feelings, emotions, and behavior, and his or her family's response, can influence the arthritis pain experience. Therefore, education about pain, pain management options, and self-management programs should be communicated to the patient and family as an integral and cost-effective part of treatment.

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Rationale for Cognitive-Behavioral Interventions

As noted earlier, people with arthritis must adapt psychologically to many stressors including pain and other symptoms. CBT can facilitate the adaptation and be useful for people who become disabled, especially by pain. Adaptation to living with pain and other aspects of arthritis may be akin to the grieving process. Loss and disruption, for example, are prominent RA-related themes (DeVellis, Patterson, Blalock, Renner, & DeVellis, 1997). The loss associated with pain is the loss of comfortable, pleasurable movement. Grieving and similar psychological processes also have been described in children and adolescents at the onset of serious chronic diseases (Geist, 1979). Such grieving processes are restorative and facilitate adaptation to a different level of comfort.

Because of complex interactions among the biological, psychological, and social factors that influence pain and function, the intensity of reported pain and the level of functioning related to pain are not totally correlated with joint damage or disease activity. Diverse factors such as educational level, age, helplessness, stressors, social support, coping style, and mood are associated with self-reports of impaired function, emotional distress, and increased pain. Changes in some of these factors can improve pain, function, and quality of life (Keefe & Bonk, 1999).

Descriptive studies with RA patients have shown that younger age is associated with increased pain levels, depression, and anxiety, whereas older age is associated with more physical disability. Mediators of these relationships are educational and income levels, stress, social support, and marital satisfaction. Psychological and physical disability appear to be influenced by negative perceptions associated with low self-esteem, low self-efficacy, and helplessness. These perceptions are, in turn, associated with ineffective coping styles such as catastrophizing, avoidance, passive coping, and denial.

These factors appear to be similar in OA, although they are not supported by as many studies. Spousal support and improved marital adjustment appear to be influential in reducing psychological disability in OA patients. Decreased self-esteem support (e.g., "Most people I know think highly of me.") and decreased belonging support (e.g., "When I feel lonely there are several people with whom I enjoy spending time.") have been associated with increased psychological disability (Weinberger, Tierney, Booher, & Hiner, 1990). Persons with RA have reported that health professionals often communicate little support in coping with pain (Shaul, 1995). Patients want health professionals to convey an understanding of their experiences without showing pity (Dildy, 1996).

A patient's adaptation to RA is influenced by success in pain management. In the early stages of disease, people with RA may "cover-up" in the face of pain and disability. Shaul (1995) identified three stages of adaptation: (a) becoming aware, (b) learning to live with RA, and (c) mastery. Mastery is a redefinition of

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normalcy and a deliberate process of decision making to manage symptoms such as pain and to balance role demands and energy. Dildy (1996) investigated suffering, a process of significant, multidimensional personal change related to RA. One study participant described her suffering experience, "It's just unreal.... I felt I was just locked in this body that was suffering and I couldn't get out.... I had been so active." Three stages of the suffering process were identified: (a) disintegration of personhood, (b) the shattered self, and (c) reconstruction of self. Whether suffering resulted from pain depended on its meaning (usually the functional limitation it produced), intensity, and controllability. Control meant making a conscious decision to change from a negative perspective to "be OK."

Depression relief is another possible indicator of success in pain management. People with arthritis have depression rates approximately 20% higher than the general public, which is a rate similar to that of people with other chronic diseases (Frank & Hagglund, 1996). Individuals who report more depressive symptoms tend to rate their pain as being greater and perceive that they have less ability to manage it (Katz, 1998).

Research on pain related to other chronic conditions has demonstrated similar complex interactions and pointed to the role of motivation in influencing the adoption of more adaptive behavioral strategies. Familiarity with effective therapies, the local resources that provide them, and an understanding of the biopsychosocial model of chronic disease will enable clinicians to promote positive adaptation in people with arthritis.

Cognitive-Behavioral Therapy

CBT is designed to reduce pain and psychological disability and to enhance pain coping. It is meant to complement, not replace, ongoing medical management of arthritis. CBT should be tailored to meet the specific needs of a person with arthritis. In using CBT methods, the clinician should take into account not only the person's pain but also his or her educational and cultural background. Although the techniques described in this section can be used individually, they are most often used in combination with each other.

Prior to CBT training, it is important to provide a rationale that helps patients better understand arthritis pain, the importance of a comprehensive approach to pain management, and the specific role that cognitive-behavioral coping strategies can play in managing pain. The goal of CBT is to help people better manage pain by changing the thoughts, feelings, and behaviors that influence their pain.

CBT provides a systematic approach for patients to learn pain-coping skills that involves a structured program of clinician instruction, guided practice, and mastery experiences. **CBT should be used to reduce pain and psychological disability and to enhance self-efficacy and pain coping.** This is especially important for people with severe, disabling pain.

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Formal training in CBT is provided by a trained psychologist, nurse, or other health professional and usually is carried out in a series of 6–10 group sessions. In each session, the clinician provides systematic instruction in pain-coping skills, and the person has an opportunity to practice skills while being given guidance and feedback. Home practice is essential to mastering pain-coping skills, and home practice assignments are provided at the end of each training session. To help people maintain their skills, training in problem solving and relapse prevention should be provided. Family members should be involved in training when possible.

Cognitive coping skills. Cognitive pain-coping skills teach people how to control pain by altering thought patterns. These skills fall into three major categories: distraction techniques, mental imagery, and cognitive restructuring.

Distraction. Distraction techniques involve actively focusing on a sensory or mental event or process to divert attention from pain. Visual distraction is one of the most commonly used forms of distraction, in which one focuses on a picture or visual scene. The focal point technique used in Lamaze childbirth preparation classes is a good example of a visual distraction. Another common method is auditory distraction (e.g., actively listening to music). Distraction also can involve mental techniques such as counting ceiling tiles.

Mental imagery. Mental imagery typically involves actively focusing on a pleasant scene and has been shown to be effective in a variety of pain populations (NIH, 1995). To use imagery effectively, a specific time should be set aside for practice, and the person should be in a relaxed and comfortable position. Imagery is more engaging when the person focuses on all of the different sensory modalities present in the image (e.g., for a beach scene one might focus on the sight of the waves, warmth of the sand, smell of the sea air, sound of the seagulls, and taste of salt on the lips).

Cognitive restructuring. Cognitive restructuring techniques help people identify, evaluate, and change maladaptive pain-related thought patterns. Individuals can learn to recognize self-defeating thoughts (e.g., "I am worthless.") that can not only influence mood (e.g., increased depression, anxiety), but also influence behavior (e.g., withdrawal from others, nonadherence to medical regimens), physiology (e.g., increased muscle tension), and environment (e.g., marital or work problems). People can learn to challenge these thoughts and restructure them by replacing them with more adaptive coping statements (e.g., "Although my arthritis pain prevents me from doing many things that are important to me, I am a worthwhile person and there are many important things I can still do.").

To ensure that people can use cognitive restructuring effectively, they should be taught how to prepare ahead of time and later use adaptive, calming thoughts when confronted with pain-producing situations. These strategies are designed to reduce not only pain, but also psychological distress, particularly depression.

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Behavioral Coping Skills

Behavioral pain-coping skills teach people to alter pain by changing their patterns of daily activity. These skills fall into three major categories: activity-pacing, pleasant activity scheduling and goal setting, and relaxation-based skills.

Activity-pacing methods. People with arthritis pain often push themselves to remain active until they are forced to stop because of severe pain. At that point, they often need prolonged rest. This cycle of overexertion, increased pain, and prolonged rest has negative consequences that include decreased tolerance for activities, anxiety, increased muscle tension, and increased reliance on pain medications. Activity-pacing methods teach people to break their daily activities into periods of moderate activity followed by limited rest. People who tend to overdo it when performing housework, for example, can learn to break it up into periods of 45 minutes of housework followed by 15 minutes of rest. Alternatively, people who are very inactive can learn to increase gradually their tolerance for activities by starting with a relatively low level of activity followed by rest and then gradually building up to higher levels of activity followed by rest. This method, based on the principle of successive approximations, is effective in helping to activate people who have become overly sedentary because of pain.

Pleasant activity scheduling and goal setting. Pleasant activity scheduling and goal setting are designed to help people increase the level and range of their daily activities. Individuals are encouraged to identify a broad range of pleasant activities and goals. They then select specific activities and goals and set a target date to accomplish them. By keeping records, people can track their progress in completion of activities and goals.

Relaxation-based skills. Relaxation-based skills teach people to control pain by deeply relaxing their muscles. A variety of relaxation techniques have been used in arthritis pain management. Progressive relaxation training teaches people to relax by slowly tensing and relaxing major muscle groups in the body starting from those in the feet and legs and progressing to those in the head and neck. In progressive relaxation training, the person learns to apply relaxation skills in daily situations in which pain is likely to be a problem (e.g., climbing stairs, transferring from a reclining to a seated position, exercising). Biofeedback is a procedure in which an electronic monitor is used to provide accurate and ongoing feedback about a bodily response such as muscle tension. The feedback enables the person to control the response (i.e., reduce muscle tension) and thereby reduce pain. Biofeedback routinely is used in conjunction with other relaxation methods.

Relapse Prevention Methods

People with arthritis often face challenging and difficult situations such as a severe pain flare. If not dealt with effectively these situations can lead to a major setback or relapse that is characterized by increased depression and a sense of

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helplessness (Keefe & Van Horn, 1993.) Relapse prevention training helps people anticipate and prepare for coping with such challenges.

Relapse prevention training is introduced early in CBT to help people develop more realistic expectations about treatment and recognize early warning signs of relapse. Helping patients to develop a written list of early warning signs of lapses and setbacks and specific problem situations that in the past have triggered a relapse can help them identify high-risk situations that might lead to a relapse. One of the most maladaptive responses to a high-risk situation is to stop active pain-coping efforts. Patients can list the pros and cons of continuing versus stopping coping strategies as a useful way to help them prevent discontinuing coping efforts. Role playing or behavioral rehearsal also is used to encourage people with arthritis to practice ways of responding to high-risk problem situations. During role playing, problematic coping strategies often can be identified and individuals can practice alternative, more adaptive ways of handling the situation. Another strategy used in relapse prevention training is self-monitoring, in which people keep track of key areas such as the frequency of practice and early warning signs of relapse. Relapse prevention contracts are routinely used in CBT. These contracts clarify expectations for daily practice and how the person will handle setbacks and relapses.

Stress Management Training

Another cognitive-behavioral approach found useful in managing arthritis pain is to include pain management as one goal in a broader cognitive-behavioral stress management program (Parler et al., 1995.) In stress management, people are taught to identify stressors, evaluate their own coping efforts, and develop new coping skills. In addition to pain management, stress management for arthritis may focus on goals such as adapting to life change, optimizing social relationships, and managing emotional distress.

As noted earlier, cognitive-behavioral interventions are used concurrently with analgesic medication in the management of arthritis pain.

Pharmacologic Management of Pain in Osteoarthritis and Rheumatoid Arthritis

Recommendations in This Section*

8. Analgesic and antiinflammatory medications are important in arthritis pain management but should be used concurrently with nutritional, physical, educational, and cognitive-behavioral interventions. (A)
9. Clinicians should consider efficacy, adverse side effects, dosing frequency, patient preference, and cost in selecting medication for pain management. (Panel consensus)

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10. For the person with OA, acetaminophen is the medication of first choice for mild pain. There is little evidence that acetaminophen provides any benefit when peripheral inflammation is a causative factor for the pain. (A) For the person with moderate to severe pain and or inflammation, a COX-2 selective NSAID is the first choice, unless the person is at significant risk for hypertension or renal disorder. (B) In persons at increased risk for hypertension and edema, clinicians should use any NSAID cautiously due to the risk of exacerbating hypertension or edema. Nonselective NSAIDs should be considered only if the person is not responsive to or not able to take COX-2 selective NSAIDs and/or acetaminophen up to 4,000 mg per day, and only after a risk analysis is done to determine the risk for a significant NSAID-induced gastrointestinal (GI) complication. If such risk factors exist, then a prophylactic agent such as a proton pump inhibitor or misoprostol should be given along with the nonselective NSAID. (B) The person at risk for a cardiovascular event should be given a regular low dose of aspirin (between 75 mg-160 mg per day), whether the patient is treated with a nonselective or COX-2 selective NSAID. (B)
11. The injection of intra-articular glucocorticoids should be considered in those persons with OA who have significantly increased and inflammatory flare or extensive inflammation in one or a few joints. Intra-articular glucocorticoids can be administered at any time during the course of the illness. (B) Systemic glucocorticoids should not be used in persons with OA. The injection of hyaluronic acid supplements into the knee may be considered in persons with OA and knee pain who are unresponsive to acetaminophen, nonselective, and COX-2 selective NSAIDs, or who cannot take these medications. Hyaluronic acid can be administered at any time during the course of the illness. (B)
12. Tramadol may be used alone or in combination with acetaminophen or NSAIDs for therapy at any time during the treatment of a person with OA when NSAIDs alone produce inadequate pain relief. (C)
13. For the person with active RA, DMARDs are the first choice of pharmacotherapy. (B,C) For the person who is receiving any of the five known DMARDs shown by radiograph to slow damage from disease progression (sulfasalazine, methotrexate, leflunomide, etanercept, and infliximab as of this writing), acetaminophen may be used as a concomitant medication for mild pain. (A) However, because RA is an inflammatory disease, many more patients will benefit from concomitant therapy with an antiinflammatory medication. A COX-2 selective NSAID should be used as a concomitant medication for the person with moderate to severe pain with or without inflammation, unless there are clear risk factors for exacerbation of renal disease or the medications are not tolerated due to GI complications. (B)

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If the antiinflammatory medication and the DMARD provide inadequate pain relief, then acetaminophen should be added. (B) If GI risk factors exist, then a prophylactic proton pump inhibitor or misoprostol should be given along with the nonselective NSAID. The person at risk for a cardiovascular event should be given a regular low dose of aspirin (between 75–160 mg per day), whether treated with a nonselective or a COX-2 selective NSAID. (B)

14. Low-dose oral glucocorticosteroids (less than 15 mg per day of prednisone or equivalent as a single dose) should be considered for short-term use in persons with RA. These medications have been shown to decrease progression of erosions for the first 2 years. When oral glucocorticosteroids are used, prophylaxis with a bisphosphonate, along with calcium supplementation and daily supplemental vitamin D to lower the risk of glucocorticoid-induced osteoporosis, should be considered. (B)
15. Intra-articular glucocorticosteroids should be used in patients with intense flares of OA or RA as evidenced by high degrees of inflammation and effusion in the joint; they can be used at any time during the course of the illness. (B)
16. Opioids should be used for patients with OA or RA when other medications and nonpharmacologic interventions produce inadequate pain relief and the patient's quality of life is affected by the pain. (B) Morphine, oxycodone, hydrocodone, or other mu agonist opioids, as a single agent or combined with an NSAID or with acetaminophen, should be used for moderate to severe OA or RA pain that has not responded to other treatments. (B) The use of codeine and propoxyphene should be avoided because of their side effects and limited analgesic effectiveness. (B)

*Please note: Recommendations appear in bold type as they are discussed in the text. See Chapter II for an explanation of the strength of the evidence supporting the recommendations.

Analgesics

Analgesic and/or antiinflammatory medications are important in arthritis pain management but should be used concurrently with nutritional, physical, educational, and cognitive-behavioral interventions. The following section discusses these medications, with an emphasis on the need to balance efficacy, adverse side effects, dosing frequency, patient preference, and cost in selecting medication for pain management.

Acetaminophen

Acetaminophen is an analgesic and antipyretic without clinically useful peripheral antiinflammatory activity (Watson, Brookes, Kirwan, & Faulkner, 2000). Pain at rest and pain at night, symptoms associated with significant inflammation, are relieved more by the use of NSAIDs. First-choice use of

acetaminophen as an analgesic in OA has been common since Bradley, Brandt, Katz, Kalasinski, and Ryan (1992) demonstrated that 1 g of acetaminophen four times a day is as effective as ibuprofen at either 1.2 g or 2.4 g per day in the treatment of patients with OA of the knee or hip. In addition, acetaminophen is better tolerated than either dose of ibuprofen. Pincus et al. (2001) demonstrated that 4 g daily of acetaminophen did not reduce pain as much as a combination product of diclofenac and misoprostol (Arthrotec 75 mg twice a day). Acetaminophen was better tolerated within the GI tract in this study.

Evidence of acetaminophen hepatotoxicity and the potential for renal damage is increasing (Barrett, 1996; Buckalew, 1996; Schiodt, 1997; U.S. Food and Drug Administration [FDA], 1997; Whitcomb, 1994; Williams, 1993). Acute overdose may cause irreversible liver damage. A recent prospective double-blind study demonstrated that giving 4 g of acetaminophen for 2 days to chronic alcoholics was no different than placebo in liver damage (Kuffner, et al., 2001). This was a small sample of patients and may not represent the population accurately. Therefore, caution is indicated for patients who take acetaminophen and drink more than two alcoholic beverages (i.e., beer, wine, or spirits) a day. If patients are ingesting more than 2 ounces of alcohol daily, the dose of acetaminophen should be decreased to a maximum of 2.5 g per 24 hr (FDA). Long-term use of acetaminophen may be associated with interstitial kidney damage or nephritis similar to that reported for the parent agent, phenacetin, leading to chronic renal failure (Perneger, Whelton, & Klag, 1994). This effect of acetaminophen is likely to be a very rare event. Note that there is a risk for both GI and liver toxicity with all OTC analgesics and NSAIDs when combined with routine heavy alcohol use.

The favorable risk-to-benefit ratio for acetaminophen in patients with mild pain who derive benefit warrants the continued use of acetaminophen in those patients. It is important for clinicians to ascertain that the patient has given the drug an adequate trial for several weeks of at least 2–3 g of acetaminophen per day before assuming that the treatment is ineffective. Patients at high risk for liver damage should be monitored every 6 months to 1 year with liver function tests (LFTs).

Nonsteroidal Antiinflammatory Drugs

NSAIDs are among the most commonly used medications, with an estimated 17 million people in the United States using them on a daily basis. The proportion of older people using them is approximately 3.6 times higher than younger people (Baum, Kennedy, & Forbes, 1985). NSAIDs are effective in the treatment of acute and chronic pain and in inflammatory musculoskeletal conditions. The recent introduction of COX-2 selective NSAIDs has improved the risk-to-benefit ratio of NSAID therapy in OA and RA in terms of GI-tract complications.

More than 20 NSAIDs, including aspirin and the COX-2 selective NSAIDs, are available in the United States. Table 11 lists these drugs by chemical subclass and by

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generic and proprietary names. Several salicylates and three nonselective NSAIDs are available as nonprescription medications. NSAIDs are effective analgesic and antiinflammatory agents, but can have adverse effects of varying degrees of seriousness. Reported adverse events with nonselective NSAIDs are more frequent than with any other prescription medication class (Table 12) (Burke, Zabinski, Pettitt, Maniadas, Maurath, & Goldstein, 2001; Gabriel & Matteson, 1995; Langman, 1988).

Commercially available NSAIDs vary in cost by a factor of seven. Nonprescription NSAIDs (e.g., ibuprofen, naproxen sodium, ketoprofen) are as effective as prescription NSAIDs when given in equivalent doses. The person's past response, cost, and dosing frequency should be major criteria when selecting from among the available NSAIDs.

Mechanism of action. NSAIDs inhibit COX, the enzyme that catalyzes the synthesis of cyclic endoperoxides from arachidonic acid to proinflammatory and other forms of prostaglandins (Simon, 1992). In the gastric mucosa, prostaglandins promote the generation of a protective barrier of mucous and bicarbonate, decrease the synthesis of gastric acid, and stimulate production of glutathione, which scavenges superoxides and promotes blood flow to the gastric mucosa (Scheiman, 1996). Prostaglandins modulate intrarenal plasma flow and electrolyte balance in the kidney (Schlondorff, 1993). The ability to inhibit COX varies among NSAIDs. There is no evidence, however, that correlates the degree of COX inhibition with antiinflammatory efficacy in individual patients.

Two isoforms of COX have been identified: COX-1 and COX-2. COX-1 is constitutive (i.e., normally present) in the gastric mucosa and is involved in the production of prostaglandins that generate the protective barrier in the gastric lumen. It also is important in modulating the extent of gastric acid production. Inhibition of COX-1 activity is a major cause of the GI toxicity of NSAIDs. COX-1 also is involved in production of prostaglandins that act in the renal parenchyma, and it is the only available isoform in platelets. COX-2 is constitutive in renal and central nervous system tissues, but of clinical importance, it is highly inducible (produced) at sites of pain and inflammation. The ideal NSAID would inhibit only induced COX-2 and exert no effect on constitutive COX-1 (Simon, 1996).

Several nonprostaglandin-mediated mechanisms of action have been demonstrated for the NSAIDs (Abramson & Weissman, 1989). NSAIDs reduce the expression of L-selectin, thus affecting a critical step in the migration of granulocytes to sites of inflammation (Diaz-Gonzalez et al., 1995). In addition, NSAIDs in vitro inhibit inducible nitric acid synthetase, which is associated with increased inflammation (Amin et al., 1995). The clinical significance of nonprostaglandin-mediated processes in inflammation is unknown. Nonacetylated salicylates are weak inhibitors of COX, but clinically appear to inhibit inflammation and pain as effectively as some NSAIDs (Blechman &

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Table 1. Dosages of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) Used to Treat People with Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis

Medication (Trade Name)	Usual 24-Hour Dose Range (adults)	Individual Dosage and Frequency (adults)		Usual Daily Dose (children) (mg/kg/24 hr)	FDA Approved Use
		Dosage	Frequency		
Acetaminophen (<i>Anacin, Excedrin, Panadol, Tempra, Tylenol, others</i>)	2-4 g	325-650 mg 650 mg-1 g	q4h q.i.d.	10-15 mg/kg/q 4-6 hr (maximum g/24 hr)	RA, OA, AS, JCA, ST
Nonselective NSAIDs					
Carboxylic Acid Derivatives (salicylic acid derivatives) Aspirin (acetylsalicylic acid) (<i>Multiple</i>)	2.4-6 g	600-1,500 mg	q.i.d.	50-100 mg/kg/24 hr/+ t.i.d.	RA, OA, AS, JCA, ST
Buffered aspirin (<i>Ascription, Bufferin, others</i>)	2.4-6 g	600-1,500 mg	q.i.d.	80-100 mg/kg/24 hr/+ t.i.d.	RA, OA, AS, JCA, ST
Enteric-coated aspirin (<i>Multiple</i>)	2.4-6 g	600-1,500 mg	q.i.d.	80-100 mg/kg/24 hr/+ t.i.d.	RA, OA, AS, JCA, ST
Choline magnesium trisalicylate (<i>Tricosal, Trisate</i>)	1.5-3 g	500-1,000 mg 750-1,500 mg	t.i.d. b.i.d.	50-65 mg/kg/24 hr + b.i.d.	RA, OA, pain, JCA
Diflunisal (<i>Dolobid</i>)	1-1.5 g	500/750 mg	b.i.d.		RA, OA, AS, JCA, ST
Salsalate (<i>Disalcid</i>)	1.5-3 g	750-1,500 mg	b.i.d.		RA, OA, AS, JCA, ST
Propionic Acid Derivatives					
Fenoprofen (<i>Nalfon</i>)	1.2-2.4 g	300-600 mg	t.i.d.		RA, OA
Flurbiprofen (<i>Ansaid</i>)	100-200 mg	50-100 mg	b.i.d.		RA, OA
Ibuprofen (<i>Advil, Motrin, others</i>)	1.2-3.2 g (for pain) 2.4-3.2 g (for inflammation)	OTC: 200-400 mg Rx: 400, 600, 800 mg Maximum: 3,200 mg	q.i.d. t.i.d.-q.i.d.	30-50 mg/kg/24 hr + t.i.d. (maximum 2.4g/24 hr)	RA, OA, JCA
Ketoprofen (<i>Orudis</i>)	75-225 mg	25-75 mg	t.i.d.		RA, OA
Naproxen (<i>Naprosyn, others</i>)	500 mg-1 g	250, 375, 500 mg	b.i.d.	10-20 mg/kg/24 hr + b.i.d.	RA, OA, JCA, ST
Naproxen Sodium (<i>Aleve, Anaprox</i>)	550-1,100 mg	275-550 mg	b.i.d.		RA, OA, ST

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Table 11. (cont.) Dosages of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) Used to Treat People with Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis

Medication (Trade Name)	Usual 24-Hour Dose Range (adults)	Individual Dosage and Frequency (adults)		Usual Daily Dose (children) (mg/kg/24 hr)	FDA Approved Use
		Usual Daily Dose	Frequency		
Nonselective NSAIDs					
Acetic Acid Derivatives Diclofenac ^a (N Arthrosc, Voltaren, others)	150–200 mg	50 mg 75 mg	t.i.d. b.i.d.	1–4 mg/kg/ 24 hr + b.i.d.	RA, OA, AS
Etoricoxib (Lodine)	400–1,200 mg	200–300 mg Maximum: 1,200 mg	b.i.d., t.i.d., q.i.d.	15–20 mg/kg/ 24 hr + b.i.d.	OA, pain
Indomethacin (Indocin, Indocin SR)	<200 mg	25–50 mg rarely >150 mg	t.i.d. or q.i.d.	2–3 mg/kg/ 24 hr + b.i.d. (max 200 mg/24 hr)	RA, OA, G, AS, JCA
Sulindac (Clinoril)	300–400 mg	150, 200 mg	q.d. b.i.d.	3–4 mg/kg/ 24 hr + b.i.d.	RA, OA, AS, ST, G
Tolmetin ^a (Tolectin, Tolectin DS)	800–1,800 mg	400, 600, 800 mg	t.i.d.	15–30 mg/ kg/24 hr + t.i.d.	RA, OA, AS, JCA
Fenamates (anthranilic acids) Meclofenamate (Meclofen)	50–400 mg	50–100 mg	t.i.d.–q.i.d.		RA, OA
Mefenamic acid (Ponstel)	1.0–2.0 g	250 mg	q.i.d.		RA, OA
Enolic Acid Derivatives Meloxicam (Mobic)	7.5–15 mg	7.5 mg (OA) 15 mg (RA)	q.d. q.d.		OA Not approved
Phenylbutazone ^b (Butazolidin)	<600 mg	100 mg	t.i.d. up to 600 mg		Severe arthritis
Piroxicam (Feldene)	10–20 mg	10, 20 mg	q.d.	0.25–0.4 mg/ kg/24 hr q.d.	RA, OA
Naphthylalkanones Nabumetone (Relafen)	1.0–1.5 g	500 mg	b.i.d. up to 1.5 g		RA, OA
COX-2 Selective NSAIDs					
Celecoxib (Celebra)	200–400 mg	100, 200 mg 200 mg	q 12 hr. q.d.		RA, OA, acute pain
Rofecoxib (VIOXX)	12.5–25 mg	12.5, 25 mg 50 mg	q.d. (chronic pain) q.d. (acute pain)		OA Acute pain

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Table 11. (cont.) Dosages of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) Used to Treat People with Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis

Medication (Trade Name)	Usual 24-Hour Dose Range (adults)	Individual Dosage and Frequency (adults)		Usual Daily Dose (children) (mg/kg/24 hr)	FDA Approved Use
		Usual Daily Dose	Frequency		
Valdecoxib (Bextra)	10 mg	10 mg	q.d.		RA, OA acute pain

^aLong acting

^bPhenylbutazone has been withdrawn from commercial availability due to markedly decreased use. This is because of serious, potentially life-threatening toxicity (i.e., blood dyscrasias). It is a potent and effective NSAID but has a higher incidence of both minor (dyspepsia) and serious adverse events than most newer NSAIDs. It is only available in infrequently compounded dosage forms.

Key: AS = ankylosing spondylitis, G = gout, JCA = juvenile chronic arthritis, OA = osteoarthritis, RA = rheumatoid arthritis, ST = soft tissue injury

Lechner, 1979; Bombardier, Peloso, & Goldsmith, 1995). Nonprostaglandin-mediated mechanisms may help to explain these clinical effects.

Adverse effects of NSAIDs. The most common adverse effect of nonselective (not COX-2 selective) NSAIDs that have been documented are GI intolerability problems including dyspepsia, abdominal pain, and nausea. Gastrointestinal mucosal damage, such as GI ulcers, bleeding, perforation, and obstruction, also is common (1%–2% ulcer complications, 2%–4% ulcer complications and symptomatic ulcers). Because platelet aggregation-mediated blood clotting is inhibited by COX-1, but not COX-2, use of COX-2 selective NSAIDs also reduces the risk of GI bleeding. Nephropathy can occur with either the COX-2 selective or the nonselective NSAIDs. Toxicities of these medications are consistent with their believed mechanism of action, the inhibition of prostaglandin synthesis. Table 12 lists potential NSAID toxicities. Table 13 lists clinically significant adverse events that occur with specific NSAIDs. NSAID gastropathy and nephropathy can be minimized by using the medications cautiously in patients with increased risk of GI and renal disorders. Good hydration is essential to minimize renal risk. Risk factors for adverse kidney effects include serious hemodynamic compromise such as hemorrhage, dehydration, moderate to severe congestive heart failure, excessive diuresis, and cirrhosis with or without ascites. Volume-depleted individuals, such as women who experience heavy menstruation and people who perspire excessively due to unusual exertion, are at increased risk as are individuals with intrinsic kidney disease. Older people with intrinsic renal disease are at increased risk of adverse renal effects from NSAIDs. The recent introduction of COX-2 selective NSAIDs (described later) provides medications that are as effective as nonselective NSAIDs, but

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Table 12. Adverse Reactions in Nonselective Nonsteroidal Antiinflammatory Drugs**Gastrointestinal**

- Nausea, vomiting, dyspepsia, diarrhea, constipation, abdominal cramps
- Gastric mucosal irritation, superficial erosions, peptic ulceration, increased fecal blood, wasting
- Major gastrointestinal hemorrhage, penetrating ulcers
- Erosions induce "diaphragm" development in small bowel
- Hepatotoxicity, hepatitis, fulminant hepatic failure

Renal

- Glomerulopathy, interstitial nephritis, alterations in renal plasma blood flow leading to a fall in glomerular filtration rate, interference with natriuresis induced by diuretics, edema, and inhibition of rennin release leading to changes in water and electrolyte balance
- Alterations in tubular function

Hematologic

- Decreased platelet aggregation possibly leading to bleeding, oozing gums, petechiae, anemia, marrow suppression, Coombs positive anemia

Central nervous system

- Headache, dizziness, confusion, hallucinations, depersonalization reactions, depression, tremor
- Aseptic meningitis, tinnitus, vertigo, neuropathy, toxic amblyopia, transient transparent corneal deposits
- Seizures

Hypersensitivity

- Asthma, asthma/urticaria syndrome, urticaria, rashes, photosensitivity, Stevens-Johnson syndrome

Respiratory

- Bronchospasm, laryngeal edema, shortness of breath

Cardiovascular

- Increased blood pressure, may reach hypertensive levels

Drug interactions

- Drug interactions such as displacement of oral hypoglycemics and warfarin from protein binding sites and from sites of metabolism
- Interferes with the actions of beta-blockers, ACE inhibitors, and some diuretics

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Table 13. Clinically Significant Adverse Effects and Costs of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) in Adults

Medication (Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b		Clinically Significant Frequent Adverse Events ^c	Special Considerations
		Lowest	Highest		
Acetaminophen (<i>Anacin, Excedrin, Panadol, Temptra, Tylenol, others</i>)	3.0 g	\$39	\$268	GI, HEM, HY, R	Risk-benefit should be considered when following medical conditions exist: alcoholism, hepatic disease, viral hepatitis, phenylketonuria, renal function impairment
Nonselective NSAIDs					
Carboxylic Acid Derivatives (salicylic acid derivatives)					Contraindications for all salicylates: Bleeding ulcers, hemophilia, angioedema, nasal polyps, associated with asthma, thrombocytopenia. Consider risk-benefit with following medical conditions: anemia, compromised cardiac function, hypertension, gastritis, gout, peptic ulcer, hepatic or renal function impairment.
Aspirin (acetylsalicylic acid) (<i>Multiple</i>)	4,200 mg	\$3	\$12	GI, HEM, HY, O	More ulcerogenic than other salicylates, associated with Reye's Syndrome, bronchospasm in asthmatics. Older people may be more susceptible to toxic effects due to decreased renal function.
Buffered aspirin (<i>Acrition, Bufferin, others</i>)	4,200 mg	\$4	\$15	GI, HEM, HY, O	Same considerations/contraindications as for all salicylates
Enteric-coated aspirin (<i>Multiple</i>)	4,200 mg	\$7	\$19	GI, HEM, HY, O	Same considerations/contraindications as for all salicylates

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Table 13. (cont.) Clinically Significant Adverse Effects and Costs of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) in Adults

Medication (Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b		Clinically Significant Frequent Adverse Events ^c	Special Considerations
		Lowest	Highest		
Choline magnesium trisalicylate ^d (Tricosol, Trisate)	2,250 mg	\$62	\$63	GI, R	Same considerations/ contraindications as for all salicylates
Diffunisal (Dolobid)	1,250 mg	\$66	\$87	CNS, GI, O	Less likely than other NSAIDs to increase presurgical bleeding and to increase bleed- ing time Higher risk than other NSAIDs in patient with renal impairment Possibility of Reye's Syndrome in children and adolescents with acute febrile disease
Salsalate (Disalcid, others)	2,250 mg	\$7	\$36	GI	Same considerations/ contraindications as for all salicylates
Propionic Acid Derivatives					⇒Risk-benefit for all NSAIDs should be considered when the following medical problems exist: asth- ma, anemia, compro- mised cardiac func- tion (CHD), edema, hypertension, renal or hepatic impair- ment, GI diseases, CHF, diabetes, sep- sis, hemophilia, SLE
Fenoprofen (Nalfon)	1,800 mg	\$40	\$46	CNS, GI, R, HY, O	Muscle cramps or pain not related to condition being treat- ed may occur.
Flurbiprofen (Ansaid)	150 mg	\$49	\$53	CNS, GI, R, O	Bloody or cloudy urine, painful & fre- quent urination may occur.
Ibuprofen (Advil, Motrin, others)	1,800 mg (for pain) 2,800 mg (for inflammation)	\$4 \$6	\$28 \$43	CNS, GI, O	May cause stomach bleeding in individuals who consume large amounts of alcohol.

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Table 13. (cont.) Clinically Significant Adverse Effects and Costs of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) in Adults

Medication (Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b		Clinically Significant Frequent Adverse Events ^c	Special Considerations
		Lowest	Highest		
Ketoprofen (Oruvail)	150 mg	\$14	\$64	CNS, GI, R	Bleeding from rectum may occur.
Naproxen (Ec-naprosyn, Naprosyn, others)	875 mg	\$69	\$82	CNS, GI, R, O	Ringling or buzzing in ears can occur. Shortness of breath or troubled breathing
Naproxen Sodium (Aleve, Anaprox)	825 mg	\$46	\$54	CNS, GI, R, O	More rapid onset but similar activity as naproxen
Acetic Acid Derivatives Diclofenac ^d (N Arthrofac, Voltaren, others)	175 mg	\$95	\$106	CNS, GI, R	⇒May precipitate acute attack of hepatic porphyria ⇒Blood dyscrasias and bone marrow depression may be induced or exacer- bated
Etorodolac ^d (Lodine)	800 mg	\$132	\$151	CNS, GI, R, O	Use with caution in people with impaired renal and hepatic func- tion, heart failure, those on diuretics, older patients
Indomethacin ^d (Indocin, Indocin SR)	137.5 mg	\$31	\$64	CNS, GI, R, O	⇒May aggravate these conditions: epilepsy, depression or other psychiatric disturbances, Parkinson's disease
Sulindac (Clinoril)	350 mg	\$58	\$72	CNS, GI, O	Use with caution when history of renal calculi and in conjunction with adequate fluid intake
Tolmetin ^d (Tolectin, Tolectin DS)	1,600 mg	\$102	\$142	CV, CNS, GI, HY, R, O	Increased blood pres- sure—may reach hypertensive levels; muscle cramps or pain may occur

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Table 13. (cont.) Clinically Significant Adverse Effects and Costs of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) in Adults

Medication (Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b		Clinically Significant Frequent Adverse Events ^c	Special Considerations
		Lowest	Highest		
Fenamates					
Meclofenamate (Meclomen)	275 mg	\$38	\$294	CNS, GI, O	
Mefenamic acid (Ponstel)	2500 mg		\$401	GI	Hypoprothrombinemia when prothrombin activity is 10%–20% of normal—increased risk of bleeding
Enolic Acid Derivatives					
Meloxicam (Mobic)	11.25 mg		\$97	GI, R	Should not use when nasal polyps associated with bronchospasm, aspirin induced present
Phenylbutazone ^d (Butazolidin)	<600 mg	\$10	\$42	HEM	Higher risk of blood dyscrasias than other NSAIDs, especially in older adults
Piroxicam (Feldene)	15 mg q day	\$53	\$63	GI	Nausea, abdominal cramps and epigastric pain may occur
Naphthylkanones					
Nabumetone (Relafen)	1,250 mg		\$108	CNS, GI, R, O	May be no safer for GI tract side effects than other nonselective NSAIDs
COX-2 Selective NSAIDs					
Celecoxib (Celebrex)	300 mg		\$134	R, CNS, GI, O	Contraindicated: severe hepatic impairment; allergic reaction to sulfonamides and aspirin; preexisting asthma; use with extreme caution if prior history of ulcer disease or GI bleeding. Older adults—adverse effects higher in older adults but safety and efficacy not different from younger patients. Lowest effective dose for shortest duration is recommended to minimize risk of GI ulceration and bleeding

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Table 13. (cont.) Clinically Significant Adverse Effects and Costs of Acetaminophen and Nonsteroidal Antiinflammatory Drugs (NSAIDs) in Adults

Medication (Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b		Clinically Significant Frequent Adverse Events ^c	Special Considerations
		Lowest	Highest		
Rofecoxib (VIOXX)	18.75 mg		\$118	R, CNS, CV, O	Contraindicated: advanced renal dis- ease; asthma or aller- gic type reactions to aspirin or other NSAIDs Use with extreme cau- tion if prior history of ulcer disease or GI bleeding; use with caution in fluid reten- tion, hypertension or heart failure
Valdecoxib (BEXTRA)	10 mg				Approved by the FDA November 2001. Not yet on the market.

^aFor medications with a range of therapeutic dosages, the midpoint between the lowest and highest doses was used to represent an average 24-hour dose.

^bAverage wholesale price, First Data Bank Price Check PC (July 2001). Costs for lowest and highest price per unit were calculated based on the average 24-hour dosage when there is more than one manufacturer. If there was only one company that produced the medication, only one cost was reported. All costs are rounded to the nearest dollar.

^cUSP DI Vol. 1, Drug Information for the Health Care Professional, 2001, ISBN 1-56353-331-0

^dLong acting

^ePhenylbutazone has been withdrawn from commercial availability due to markedly decreased use. This is because of serious, potentially life-threatening toxicity (i.e., blood dyscrasias). It is a potent and effective NSAID but has a higher incidence of both minor (dyspepsia) and serious adverse events than most newer NSAIDs. It is only available in extemporaneously compounded dosage forms.

Key: The following symbols mean that an adverse effect occurs frequently (3%–8%) with the specific drug:

CNS = central nervous system; CV = cardiovascular; GI = gastrointestinal; HEM = hematologic; HY = hypersensitivity; R = renal; O = other

⇒ = Major clinical significance

that have less risk of gastroduodenal mucosal damage or bleeding. There is no evidence that COX-2 selective NSAIDs produce any less renal toxicity than nonselective NSAIDs.

NSAID use in OA. Half of all NSAIDs used by older adults in this country are for pain due to OA (Flynn, 1994). There is no evidence that any NSAID improves or alters the pathophysiology of joint destruction in OA. There are some data on certain NSAIDs such as indomethacin that indicate the drug worsens cartilage metabolism, thus accelerating cartilage damage in OA. They do reduce pain, decrease the gel phenomenon, and improve function in OA patients, but it is unclear if this is due to antiinflammatory or analgesic activity (Murray & Brater, 1990). An unresolved question is whether NSAIDs (either

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COX-2 selective or nonselective) are superior to acetaminophen for OA pain relief. This question is important considering the toxicities of NSAIDs, especially in older patients.

NSAID use in RA. NSAIDs effectively reduce the pain and inflammation due to RA. Some investigators suggest that NSAID therapy also may affect the underlying pathophysiologic mechanism of RA as evidenced by significant reductions in rheumatoid factor (RF) levels and C-reactive protein (CRP) levels observed in clinical trials (Cush, Lipsky, Postlethwaite, Schrohenloher, Saway, & Koopman, 1990). There is, however, no evidence to suggest that NSAIDs are disease modifying. Therefore, drugs that are disease modifying (DMARDs) and that have been shown to reduce pain (e.g., sulfasalazine, methotrexate, leflunomide, etanercept, infliximab) are the drugs of first choice. The COX-2 selective NSAIDs should be used as additional analgesic and antiinflammatory agents if needed, unless the patient is at increased risk for significant hypertension or renal disease or does not respond to COX-2 selective NSAIDs. In either of these cases, the nonselective NSAIDs should be considered; however, the effects on hypertension or the kidneys may be the same.

Efficacy and safety of COX-2 selective NSAIDs. The discovery of COX-2, a second isoform of COX, led to the development of NSAIDs with the same analgesic and antiinflammatory activity as nonselective NSAIDs without the inherent risk of gastroduodenal mucosal damage and impaired platelet aggregation mediated by the inhibition of COX-1. COX-2 selective NSAIDs also appear to have no effects on platelets at efficacious therapeutic doses because COX-1 is the only prostaglandin isoform in the platelet. The first COX-2 selective NSAID, celecoxib, improved pain and inflammation as effectively as naproxen (500 mg twice a day) in short-term therapy (Simon et al., 1998). There were no platelet effects or evidence of upper GI mucosal damage after 7 days of therapy. Celecoxib at any dose had an incidence of gastroduodenal ulcers 3 mm or larger, which was no different from the effects of placebo, whereas participants treated with naproxen (1,000 mg per day) had ulcers greater than 3 mm with obvious depth.

Studies of the second COX-2 selective NSAID, rofecoxib, in patients with acute pain demonstrated that 25–50 mg produced pain relief within 45 minutes, was consistently better than placebo, and was as effective and had a longer duration of action than ibuprofen (Ehrich, Dallob et al., 1999). Both rofecoxib (12.5 and 25 mg) and celecoxib (100 mg twice a day or 200 mg daily) have been shown to be as effective as ibuprofen (2.4 g daily), diclofenac (150 mg daily), naproxen (1 g daily), and acetaminophen (1 g daily) in the treatment of a heterogeneous population of patients with OA (Cannon, 2000; Ehrich, Schnitzer, Kamin, & Olson, 1999; Silverstein et al., 2000; Zhao et al., 1999). A recent study (Geba, Weaver, Polis, Dixon, & Schnitzer 2002) demonstrated that COX-2 selective NSAIDs are superior to acetaminophen for moderate to severe pain.

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Treatment response is similar to responses observed with nonselective NSAIDs in many randomized clinical trials conducted prior to introduction of the COX-2 agents; about 35% of all patients do not respond. According to Simon et al. (1999), in the treatment of patients with RA, celecoxib (100 mg twice a day and/or 200 mg daily) was shown to be as effective as naproxen (1 g per day) and diclofenac (150 mg per day). Celecoxib was approved by the FDA for the treatment of the signs and symptoms of RA, and rofecoxib is in clinical trials to determine its effectiveness in treating RA pain.

When evaluated in both short-term and 6- to 12-week efficacy trials in OA patients, celecoxib and rofecoxib were equally safe. Each caused dyspepsia, abdominal pain, and nausea slightly more frequently than placebo but less frequently than nonselective NSAIDs. Clinical trials demonstrated a decreased incidence of upper GI mucosal damage with the COX-2 selective agents as measured by endoscopy. Similarly, clinical trials demonstrated that the COX-2 selective agents are safer than nonselective NSAIDs in production of ulcers as measured by endoscopy. Randomized controlled trials (RCTs) with large sample sizes have demonstrated that 50 mg rofecoxib four times a day (2-4 times the treatment dose in OA) (Bombardier et al., 2000) and 400 mg twice a day of celecoxib (2-4 times the treatment doses of RA and OA, respectively) (Silverstein et al., 2000) produced 2-3 times fewer symptomatic ulcers and ulcer complications (e.g. bleeding, perforation, obstruction) than did 500 mg twice a day of naproxen or 800 mg three times a day of ibuprofen, respectively.

RCTs of both COX-2 selective NSAIDs showed that at doses used to treat OA, the incidence of hypertension and peripheral edema was the same for rofecoxib and celecoxib as for nonselective NSAIDs. When celecoxib was used to treat RA there was no noted increase in pedal edema or hypertension at doses of 100, 200, or 400 mg twice a day (Simon et al., 1999). The use of rofecoxib at 50 mg per day for longer than 5 days caused a 6.3% incidence of peripheral edema and an 8.3% incidence of hypertension. Preliminary studies of 50 mg of rofecoxib daily for 6 weeks in the treatment of patients with RA demonstrated no increased incidence of either hypertension or peripheral edema (Schnitzer et al., 1999). Until data are obtained from patients who are at risk for renal complications, it would be wise to avoid COX-2 selective medications as well as nonselective NSAID therapy in patients with a creatinine clearance of less than 30 ml per minute.

There have been concerns that inhibition of COX-2 without inhibition of COX-1 might lead to an increased propensity for thrombosis in patients who are at risk. The two large studies of GI complications for rofecoxib and celecoxib (Bombardier et al., 2000; Silverstein et al., 2000) partially addressed this issue. In the approximately 8,000 patients with RA who were treated with rofecoxib 50 mg per day or naproxen 1,000 mg per day, there was a statistically significant

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increase in nonfatal myocardial infarctions (MIs) in patients treated with rofecoxib compared with those treated with naproxen (0.5% with rofecoxib and 0.1% with naproxen). Whether this observation is due to cardioprotection afforded by the relatively long-acting NSAID through its effects on the platelets or was due to a prothrombotic tendency of rofecoxib is indeterminable by this study. The celecoxib study does not help to clarify the issue. In the celecoxib study of approximately 8,000 patients with RA or OA, about 20%-22% of the patients were concomitantly on low-dose aspirin and about 40% of the patients had a history of cardiovascular disease. There were about the same number of patients in the rofecoxib study with a prior history of cardiovascular disease, but aspirin at any dose was not allowed in the rofecoxib versus naproxen study. In the celecoxib long-term outcome trial there was no difference in nonfatal MIs in patients treated with celecoxib 400 mg (2-4 times the treating dose of RA and OA, respectively) as compared with patients treated with ibuprofen (800 mg) or diclofenac (75 mg) with or without low-dose aspirin. Both ibuprofen and diclofenac have prominent COX-1 effects, but only diclofenac has a relatively long half-life similar to that of naproxen. The similarities of nonfatal MIs in celecoxib, ibuprofen, and diclofenac were observed only when those patients not on aspirin (about 78%) were analyzed (Silverman et al., 2000).

We do not know from these studies whether there is an increased risk for clinically significant thrombosis with COX-2 selective NSAIDs. It is clear that if patients are at risk for thrombosis, then low-dose aspirin is the appropriate therapy. When the patient is treated with a COX-2 selective or nonselective NSAID is required, the low-dose aspirin should be taken along with the NSAID. There is no evidence that long-acting nonselective NSAIDs are cardioprotective.

A secondary analysis of data from previous studies suggested that there may be an increase of cardiac events in patients who use a COX-2 selective NSAID due to its inherent lack of effect on platelet COX (Mukherjee, Nissen, & Topol, 2001). Drug manufacturers, clinical investigators, and others have criticized the methods used in the secondary data analysis and question the conclusions. Clearly more information is needed before conclusions can be drawn. A prospective trial would be helpful in evaluating and determining risk. **Any patients who are at risk for a cardiac event and are treated with either a nonselective NSAID or a COX-2 selective NSAID should also receive low-dose aspirin.**

Meloxicam is marketed as a COX-2 selective NSAID but it has higher COX-1 inhibiting effects than either celecoxib and rofecoxib at therapeutic doses. That is, it may inhibit COX-1 at higher therapeutic doses (Dequeker et al., 1998). There is evidence that meloxicam is as effective as other NSAIDs (Lund, Distel, & Bluhmki, 1998). In two short-term trials of the safety of meloxicam, large numbers of patients who were treated demonstrated pain relief with minimal toxic effects. Because no patient was studied for more than 30 days, safety

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with long-term use is unknown. There are conflicting data regarding the effect of meloxicam on platelet activity (Panara et al., 1999). See Chapter II for a table of evidence on the COX-2 selective NSAIDs.

Valdecoxib (BEXTRA) was approved by the FDA at the time that this guideline was going to press. Valdecoxib is approved for pain and inflammation due to OA and RA at a dose of 10 mg daily. The FDA-approved labeling contains no reference to edema or exacerbation of hypertension.

NSAID selection. At equipotent doses, the efficacy of all NSAIDs is similar across patient populations, but responsiveness of individual patients with OA and RA to specific NSAIDs differs (Cush, Jasin, Johnson, & Lipsky, 1990). This differential effect may not be as apparent when NSAIDs are combined with other analgesics such as opioids. It is not possible to predict an individual's responsiveness to a specific NSAID. Therefore, serial trials of different NSAIDs at full doses for at least 2 weeks are indicated for patients who do not respond to the first NSAID tried.

NSAIDs often are subdivided into chemical subclasses that are listed in Table 11. There is no evidence that any chemical subclass of NSAID is superior to any other subclass. Individual NSAIDs within several of the classes may be better or more poorly tolerated by an individual patient. For a given patient, lack of response to one NSAID does not preclude a response to another drug from the same chemical subclass or to an NSAID from another subclass. The determinants of individual patient responsiveness to NSAIDs are not understood. Possible reasons include variable absorption and bioavailability of the medication; patient adherence to the prescribed regimen; other biological effects of the NSAIDs, which may be variably expressed; the metabolism and excretion of the active agent; and perhaps genetic polymorphism.

Clinicians should consider efficacy, adverse side effects of NSAIDs (especially GI and renal), dosing frequency, patient preference, and cost when selecting medications for pain management. For example, although aspirin is inexpensive, its frequent dosing makes it inconvenient, and it is associated with the highest incidence of adverse gastric effects. Dyspepsia results from contact of drug with the gastric mucosa. Enteric coated aspirin reduces local gastritis (but not systemic gastropathy) but absorption is delayed and often variable. Enteric coated aspirin also is much more expensive than compressed tablets. Traditional use and indication-directed marketing of specific NSAIDs often influence selection, but there is rarely evidence to support that any one NSAID is better than another for such indications.

Individual patient characteristics may favor the selection of a particular NSAID. For instance, in patients with a history of asthma, nasal polyps, and aspirin sensitivity, nonacetylated salicylates are safer than most other NSAIDs (Szczeklik, Nizankowska, & Dworski, 1990). It is unknown whether the COX-2

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selective medications will be safer. Close monitoring still is required because of the potential for cross-sensitivity.

Pharmacokinetic properties of NSAIDs also influence selection. NSAIDs with short time to peak serum concentration are best suited for treatment of acute musculoskeletal pain because of their more rapid onset of action, and NSAIDs with longer half-lives are more appropriate for long-term use in people with arthritis. NSAIDs requiring less frequent dosing possibly improve adherence, but once-daily NSAID dosage preparations should be used with caution in older persons and in people with hepatic or renal impairment.

The antiinflammatory and analgesic benefits of NSAIDs must be weighed against their potential risks, particularly in older people (Goodman & Simon, 1994). Overall risk includes the risk that patients have from other medical conditions, with significant comorbidity most prevalent in older adults.

Costs and benefits of NSAIDs. It is important that clinicians consider the relationships among effectiveness, adverse side effects, patient preference, and cost of various NSAIDs alone and in combination with gastroprotective agents. As noted, at equipotent doses the effectiveness of all NSAIDs is similar across patient populations although response of individual patients to specific NSAIDs can vary. Table 13 shows costs (First Data Bank Price Check PC, 2001) and adverse effects (as reported in clinical trials and epidemiologic studies) of various NSAIDs. There have been few studies of patient preference, but some evidence of this factor is provided by withdrawals from clinical trials because of adverse reactions.

Studies published in peer-reviewed journals or peer-reviewed supplements have used evidence from clinical trials and outcome studies to describe clinical and cost outcomes of various NSAIDs (e.g., Burke et al., 2001; Gabriel & Matteson, 1995). The authors make clear the need to balance the costs of the medication with the costs of preventing or treating adverse events (Chancellor, Hunsche, de Cruz, & Sarasin, 2001), and they provide some evidence for the cost-effectiveness of the COX-2 selective NSAIDs in the management of arthritis pain. The COX-2 selective NSAIDs, for example, are less expensive and produce fewer adverse effects than the combination of a nonselective NSAID with misoprostol or a proton pump inhibitor. (See Tables 13 and 14.)

The cost-to-benefit ratio should be considered in the use of the COX-2 selective NSAIDs. Although the COX-2 selective NSAIDs are safer than the nonselective NSAIDs in terms of GI-tract toxicity, the COX-2 selective NSAIDs are no more effective and they are no more safe to the kidney. They are useful primarily for people who have chronic illnesses needing long-term treatment and who are at increased risk for a potential GI complication with a nonselective NSAID.

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The American College of Rheumatology (2000) guidelines on medical management of OA of the hip and knee noted the need for recommendations for therapy to be modified as new knowledge of the disease is gained and new therapies become available. Evaluation of the benefits of emerging treatments should be balanced with consideration of adverse effects, patient preference, and costs.

Table 14. Clinically Significant Adverse Effects and Costs of Gastroprotective Medications in Adults

Medication (Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b	Clinically Significant Frequent Adverse Events ^c	Special Considerations
Gastroprotective Lansoprazole (Prevacid)	15 mg	\$118	GI, CNS, CV, HEM	Reduce dosage in impaired hepatic function.
Misoprostol (Cytotec)	800 mcg	\$128	CV, GI, CNS	⇒Risk-benefit should be consid- ered when the fol- lowing medical problems exist: CVA, coronary artery disease, epilepsy, inflamma- tory bowel disease, sensitivity to prostaglandins
Omeprazole (Losec, Prilosec)	20 mg 40 mg	\$178		Dosage adjustments should be consid- ered for Asian patients. ⇒Risk-benefit should be consid- ered when hepatic disease present.

^aFor medications with a range of therapeutic dosages, the midpoint between the lowest dose and highest dose was used to represent an average 24-hour dose.

^bAverage wholesale price, First Data Bank Price Check PC (July 2001). All costs are rounded to the nearest dollar.

^cUSP DI Vol. 1, Drug Information for the Health Care Professional, 2001, ISBN 1-56363-331-0

Key: The following symbols mean that an adverse effect occurs frequently (3-9%) with the specific drug.
CNS = central nervous system, CV = cardiovascular, GI = gastrointestinal, HEM = hematologic
⇒ = Major clinical significance

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Topical Agents

Application of ointments and counterirritant rubs such as menthol, other liniments, and rubbing alcohol to painful joints and muscles is a common self-management practice. These preparations have a chemically produced counterirritant effect (Nicholas, 1994). Capsaicin, an enzyme found in hot peppers, achieves neuromodulatory effects. Capsaicin is more effective than analgesic balms (e.g., topical liniments such as menthol) when the patient can use it long enough to become tolerant to the burning side effect. Controlled trials of capsaicin in patients with OA and RA found significant benefit in both conditions (Deal et al., 1991) and relief of hand pain in OA, but not in RA (McCarthy & McCarty, 1992). When capsaicin containing cream or lotion is applied to a painful area several times a day for several weeks, it depletes the pain facilitator substance P (Schnitzer, 1998). Capsaicin is not effective if applied when symptoms occur; its therapeutic effect depends on regular four-times-a-day application. The application of the preparation, including massaging the skin, may contribute to its analgesic effect. Toxicity is minimal, but local irritation is common, especially at the beginning of therapy. Hands should be washed well immediately after applying the medication to prevent accidental exposure to mucous membranes or eyes.

Hyaluronic Acid Viscosupplementation for Osteoarthritis

Synovial fluid hyaluronic acid (HA) is decreased in patients with OA. Replacement with either synthetic or biologically derived HA is thought to diminish pain in OA of the knee with little evidence of beneficial effects on articular cartilage (Adams et al., 1995).

The synovial lining cell layer produces a highly viscous lubricating fluid—synovial fluid—which consists of high molecular weight substances, such as HA and lubricin (Hilbert et al., 1985). Those substances coat the hyaline cartilage surface thereby providing lubrication during movement. The highly viscous nature of the synovial fluid is important in providing a nearly frictionless surface for joint movement. Although lubricin may play an important role in cartilage-on-cartilage lubrication, HA, which also is highly viscous, plays an important role in the movement of soft tissues, such as with the movement of adjacent synovial folds over each other (Dougados, Nguyen, Litrar, & Amor, 1993).

The viscoelasticity (or elastoviscosity) of HA is one of its most important physical characteristics, allowing synovial fluid to function differently under varying conditions of load bearing. In the presence of low-shear stresses, HA provides high viscosity and low elasticity, whereas at high-shear stresses, it becomes more elastic and absorbs energy more efficiently, thus improving the mechanical performance of the joint. As more inflammation develops in an osteoarthritic joint, more damage ensues. Subsequently, less HA is synthesized, and that which is synthesized in the OA joint is of poorer quality, providing less viscoelasticity. It has been hypothesized that the introduction of replacement HA of sufficiently high

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molecular weight would delay, if not halt, the progression of OA. This process has been well documented in experimental animal OA models (Pozo, Balazs, & Belmonte, 1997), but human evidence is lacking.

Intra-articular HA injection is referred to as "viscosupplementation," a process whereby exogenous HA (or similar high molecular weight substances) provides a replacement for the lubrication that has been lost due to the disease. It is FDA approved for the treatment of knee pain in OA patients who are unresponsive to nonpharmacologic measures and analgesic medications. Because the agent is isolated from rooster combs, people who are allergic to chickens or eggs should not receive it.

Two formulations of HA for intra-articular injection are available for the symptomatic treatment of patients with knee OA and a third is in clinical studies. (See Table 15.) The two commercially available products differ considerably with respect to molecular weight. Hyaluronate sodium (Synvisc), the higher molecular weight product, is produced by chemically crosslinking individual HA molecules with formaldehyde and vinylsulfone to give larger molecules of about 6×10^6 daltons (or 600 kDa) in molecular weight. HA (Hyalgan) has a molecular weight of about 5×10^5 daltons (or 500 kDa) and is not crosslinked. Some investigators and clinicians believe that using the higher molecular weight HA sup-

Table 15. Dosage and Cost Data for Hyaluronic Acid Supplementation Therapies

Medication (Trade Name)	Dosage	Cost of Medication*	Special Considerations
Hyaluronate sodium derivative (Synvisc)	3 injections of 2 mg/ injection each week for 3 sequential weeks	1 injection = \$113 x 3 = \$339 ^b	People with known sensitivity to hyaluronate sodium, avian proteins, feathers, and egg products may be sensitive to this. Should be used only in knee joints. Knee pain, pain at injection site, and swelling of the knee may occur.
Hyaluronic Acid (Hyalgan)	5 injections of 2 mg/ injection each week for 5 sequential weeks	1 injection = \$72 x 5 = \$360	People with hypersensitivity to avian proteins, feathers, and egg products may also be sensitive to this. Should be used only in knee joints. Allergic reaction and anaphylac- toid reaction can occur but are infrequent.

*Average wholesale price, First Data Bank Price Check PC (July 2007).

^bAll costs are rounded to the nearest dollar.

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plementation is critical to obtain positive clinical effects. It has been described that crosslinking the HA leads to improved elasticity and lubrication, longer retention within the joint, and increased resistance to degradation by the available free radicals in the actively inflamed joint affected by OA. Use of the crosslinked product has been reported to be associated with rare postinjection flares (Lohmander et al., 1996). For the lower molecular weight HA, two cases of anaphylaxis in 5 million injections were reported (Lohmander et al.). Because therapy requires multiple injections, the costs of the HA product, the required weekly visits, and the injection are substantial.

The injection of intra-articular glucocorticoids should be considered in those persons with OA who have significantly increased and inflammatory flare or extensive inflammation in one or a few joints. Intra-articular glucocorticoids can be administered at any time during the course of the illness. (B) Systemic glucocorticoids should not be used in persons with OA.

The injection of HA supplements into the knee may be considered in persons with OA and knee pain who are unresponsive to acetaminophen, nonselective, and COX-2 selective NSAIDs, or who cannot take these medications. Hyaluronic acid can be administered at any time during the course of the illness.

Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis

RA is a systemic, inflammatory and erosive disease that may lead to significant damage of the diarthrodial joints. First-line pharmacotherapy with analgesics and antiinflammatory agents is insufficient unless the person has only mild disease or spontaneously achieves a remission. Almost all people with RA require pharmacotherapy with DMARDs, which may delay disease progression, or alternatively, may alter the natural history of the disease. These medications also have been shown to be effective in decreasing chronic pain. DMARDs are listed in Table 16.

A clinical response to a DMARD may take weeks or months to develop, and the potential toxicity of some DMARDs is high. Frequent clinician visits and even more frequent blood and urine monitoring are required for some DMARDs to ensure their safe use. Clinicians in consultation with patients should balance the effectiveness of these agents with their costs, the surveillance required, and the therapy needed if a toxic event occurs.

Hydroxychloroquine (Plaquenil) is one of the best tolerated DMARDs, but often is only a useful adjunct to other DMARDs; it is rarely effective alone. The usual dose is 200 mg twice a day to start, subsequently decreased to once daily. The major toxicity is increased retinal pigmentation, which, if undiscovered, may lead to blindness. Ophthalmologic examination is indicated about every 6 months. Early discontinuation of the drug allows the process to reverse, although reversal is not always possible (Kremer, 2000). Loss of color vision often precedes extensive retinal damage.

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Table 16. Disease-Modifying Antirheumatic Drugs (DMARDs) and Dosages			
Medication (Trade Name)	Usual Adult Dosage	Usual Pediatric Dosage	Comments and Special Considerations
Azathioprine (Imuran)	PO: 50 mg up to 200 mg/24 hr	PO 2–3 mg/kg q.d.	Not associated with improved out- come as measured by radiograph
Cyclophosphamide (Cytoxan, Neosar, Pocytex)	PO or parenterally: 1–2 mg/kg	PO 1–2 mg/kg q day or IV: 500– 1000 mg/m ² IV monthly	Experimental and highly toxic Limited by associated leukemia, urinary tract cancers
Cyclosporine (Neoral, Sandimmune, Sang-cya)	3–5 mg/kg/ 24 hr	PO 3–5 mg/kg divided b.i.d.	Trough level between 100 and 200 mg Use with caution in people with impaired renal or hepatic function, hypertension, and kidney dysfunc- tion
D-penicillamine (Cuprimine, Depen)	PO: 75 mg–125 mg to start, raising dose by 125 mg q 3 wks until 750 mg	PO 5–10 mg/kg q day Maximum daily dose = 750 mg	Rarely used because of toxicity
Etanercept (Enbrel, Enbrel)	SQ: 25 mg 2x/wk	SQ 0.4 mg/kg 2x/wk up to 25 mg	Soluble receptor to TNF- α Use with caution in history of recurring infections
Hydroxychloroquine (Plaquenil)	PO: 200 mg b.i.d. to start then 200 mg q.d.	PO <6.5 mg/kg q.d.	Retinal toxicity most important problem
Infliximab (Remicade)	IV: 3 mg/kg q 4–6 wks up to 10 mg/kg	IV: 3–5 mg/kg (rounded up to nearest 100) q 8 wks (maintenance)	(Monoclonalab to TNF- α) Use with caution in older adults
Intramuscular/Oral Gold Auranofin (Myochrysin, Ridaura, Solganol)	IM: 10 mg q wk, then 25 mg q wk, then 50 mg q wk; decrease to q mo. PO: 3–10 mg PO q.d.	IM: 0.5–1 mg/kg weekly Maximum weekly dose 50 mg PO: 0.5 mg/kg q.d. maximum 9 mg	Risk of severe reactions; generally not used in children Heavy metal toxic reactions Diarrhea
Leflunomide (Arava)	PO: 100 mg q.d. x 3 days then 10 or 20 mg q.d.	Too little data in children to specify dosage	Liver toxicity, rare
Methotrexate (Folex, Folex PFS, Mexate, Mexate-AQ, Rheumatrex)	PO, SQ, or IM: 7.5–15.0 mg q wk up to 40 mg q wk 1 q b.i.d. to q.i.d.	PO: 0.5–1.0 mg/kg q wk 10–20 mg/m ² /wk up to 1 mg/kg/wk	Oral ulcers, liver, pulmonary, and bone marrow toxicity can occur Teratogenic

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Table 16. (cont.) Disease-Modifying Antirheumatic Drugs (DMARDs) and Dosages			
Medication (Trade Name)	Usual Adult Dosage	Usual Pediatric Dosage	Comments and Special Considerations
Sulfasalazine (Axi-Sulfasalazine, Azulfidine, PMS- Sulfasalazine, Salsazopyrin)	PO: 1 g b.i.d. to q.i.d. b.i.d. up to 4 g/d	PO: 40–60 mg/kg divided b.i.d.	Sulfa allergy is contraindication Enteric coated is better tolerated

Key: IM = intramuscularly, IV = intravenously, PO = orally, SQ = subcutaneously

Methotrexate, orally or parenterally, is one of the more effective agents in reducing RA symptoms. Furthermore, methotrexate has been shown to slow progression of damage as measured by radiograph in patients who respond to therapy, although remissions have not been reported with either short- or long-term therapy. Methotrexate acts quickly (approximately 8 weeks) and usually is administered weekly with the average dose between 7.5 and 15 mg; however, doses to 25 mg weekly have been used. Careful monitoring is essential to minimize toxicity, and untoward pulmonary events can occur despite monitoring. The most common toxic reactions are nausea and mouth sores. The mouth sores can be effectively inhibited by administering 1 mg of folic acid daily concomitantly. Other relatively frequent adverse events include medication-induced hepatitis or fibrotic liver damage and macrocytic red blood cell changes. LFTs should be monitored regularly, and if transaminases are consistently above normal for 4–6 months after the first 6 months of therapy, liver biopsy should be considered. Furthermore, if there are several elevations of LFTs, the dose should be decreased. Patients should be instructed not to drink alcohol while taking methotrexate. The erythrocyte sedimentation rate decreases and anemia often improves on this therapy, but rarely do they return to normal. After methotrexate is discontinued, a flare of the disease usually occurs within 1 month. Over time it is not unusual to require a higher dose to maintain the same response.

Parenteral gold therapy is one of the few pharmacologic therapies associated with true remission. Such remissions, however, are rare and more than 40% of patients do not tolerate the therapy because of toxic effects. Dosing is weekly (25–50 mg intramuscular [IM] after a test dose of 10 mg followed by 25 mg IM). When parenteral gold therapy works, effects may not be seen for 3–6 months after initiation of therapy. Once an effect is achieved, a maintenance dose of 25–50 mg every month can be attempted. Common toxic reactions with parenteral gold include heavy metal renal damage consisting of proteinuria and an active urinary sediment and/or bone marrow suppression. Blood counts and urinalysis are required before each dose is administered. Oral gold therapy has been demonstrated to work in only a few studies. The delay in onset of effect may approach

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9–10 months, and more than 25% of patients suffer intolerable diarrhea.

Sulfasalazine is commonly used in Europe to treat early RA, but American studies have demonstrated only a moderate effect on slowing joint damage. Smolen et al. (1999) demonstrated that sulfasalazine was as effective as methotrexate and leflunomide at delaying progressive joint damage. The usual dose is 2–4 g in divided doses (1 g twice a day to four times a day) initially, with maintenance therapy at about 2 g per day (1 g twice a day).

Three other drugs identified as DMARDs are leflunomide and two TNF- α inhibitors: infliximab and etanercept. Leflunomide is an oral agent that inhibits T cell function. It inhibits dihydroorotate, which decreases the clonal expansion of T cells. It is available as a 20 mg daily tablet with some clinicians using a 3-day loading dose of 100 mg per day. It is possible that this dose might increase the incidence of hepatotoxicity. Leflunomide has been shown to improve the signs and symptoms of RA as measured at 6 months and at 2 years. It has been shown to improve health-related quality of life and to decrease the progression of damage as measured by radiograph (Sharp, Strand, Leung, Hurley, & Loew-Friedrich, 2000). There is a potential for hepatotoxicity such as with methotrexate. It also can affect the bone marrow, but there is no evidence of potential pulmonary damage or fibrosis.

The two TNF- α inhibitors have become important choices for therapy, although less is known about them than the other drugs. Etanercept is the human p75 TNF- α receptor product that includes a human Fc portion of an immunoglobulin. Two subcutaneous injections per week provide enough circulating material to bind circulating TNF- α . It also modulates lymphotoxin- α . Studies have shown that signs and symptoms of RA improve by about 60%–70% as measured by a composite outcome score (American College of Rheumatology [ACR] 20) in both earlier and later disease. Etanercept can be given with or without other drugs such as methotrexate. It has been shown to improve health-related quality of life and to decrease progression of disease as measured by radiograph.

Infliximab is a humanized monoclonal antibody to TNF- α including a human Fc fragment of immunoglobulin and a mouse hypervariable region. This biologic response modifier is administered by infusion every 4–8 weeks after an initial loading period. Most RA studies have used concomitant methotrexate weekly. This combination has been shown to decrease the symptoms and signs of RA by about 60%–70% as measured by ACR 20. It also has been shown to improve health-related quality of life and to decrease disease progression as measured by radiograph.

Both etanercept and infliximab as biologic response modifiers have reasonable evidence for safety. There appears to be local irritation associated with the subcutaneous injection of etanercept or with intravenous infusion of infliximab. Both drugs are associated with an increased incidence of tuberculosis infections,

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listeria infections, and fungal infections. Several cases of demyelinating disease have been associated with the use of etanercept. It is unknown whether these biologic therapies have more risk for inducing lymphoma or other forms of malignancy in patients than the known risks associated with methotrexate and other chemotherapies in the treatment of RA.

For the person with active RA, DMARDs are the first choice of pharmacotherapy. For the person who is receiving any of the five known DMARDs shown by radiograph to slow damage from disease progression (sulfasalazine, methotrexate, leflunomide, etanercept, and infliximab as of this writing), acetaminophen may be used as a concomitant medication for mild pain. However, because RA is an inflammatory disease, many more patients will benefit from concomitant therapy with an antiinflammatory medication. A COX-2 selective NSAID should be used as a concomitant medication for the patient with moderate to severe pain with or without inflammation, unless there are clear risk factors for exacerbation of renal disease or the medications are not tolerated due to GI complications. If the antiinflammatory medication and the DMARD provide inadequate pain relief, then acetaminophen should be added. (B) If GI risk factors exist, then a prophylactic proton pump inhibitor or misoprostol should be given along with the nonselective NSAID. The person at risk for a cardiovascular event should be given a regular low dose of aspirin (between 75–160 mg per day), whether treated with a nonselective or a COX-2 selective NSAID.

Other DMARDs include D-penicillamine, which has been reported to be as effective as parenteral gold therapy by some investigators, but is more toxic than gold therapy and therefore rarely used. Certain antineoplastic agents have been used as immunomodulators in the management of severe RA. Principal among these are azathioprine and cyclophosphamide, both of which can cause malignancy. Cyclosporine is effective at a 3–5 mg/kg dose, but renal toxicity and hypertension limit its use. Combination chemotherapy (e.g., methotrexate and cyclosporine or hydroxychloroquine, sulfasalazine and methotrexate) is currently under investigation for its usefulness in RA.

Systemic Glucocorticosteroids

Low-dose oral glucocorticosteroids (less than 15 mg per day of prednisone or equivalent as a single dose) should be considered for short-term use in persons with RA. These medications have been shown to decrease progression of erosions for the first 2 years. When oral glucocorticoids are used, prophylaxis with a bisphosphonate, along with calcium supplementation and daily supplemental vitamin D to lower the risk of glucocorticoid-induced osteoporosis, should be considered.

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Systemic glucocorticosteroid therapy is used with some patients with RA, most commonly at a dose of 10 mg or less of prednisone equivalent per day. Long-term adverse effects limit the long-term use of steroids, and there is little evidence that they are effective in altering the natural history of the disease during long-term therapy (Kirwan & Rankin, 1997).

Intra-articular Glucocorticoids

For patients with prominent inflammation in one or two joints, intra-articular glucocorticoid injection may be helpful. Crystalline preparations provide prolonged retention in the joint. Injections should not be repeated more than 3–5 times per year in any one joint. There is a risk of local infection and of a transient inflammatory response believed to be due to the glucocorticoid crystals that can be indistinguishable clinically from an infection or a flare of arthritis (Leardini, Perbellini, Franceschini, & Mattara, 1988). Other toxic effects include transient insulin resistance with repeated injections into a single joint, inhibition of new bone formation, and increased bone loss (Murray, DeBowes, Gaughan, Zhu, & Arthanasiou, 1998). There are no studies that compare available glucocorticoid injection formulations.

Intra-articular glucocorticoids should be used in patients with intense flares of OA or RA as evidenced by high degrees of inflammation and effusion in the joint; they can be used at any time during the course of the illness.

Opioids

Opioid analgesics have long been accepted as highly effective analgesics in the management of acute and cancer-related pain. Prior to the 1990s, opioids were not commonly accepted as analgesics in chronic nonmalignant pain, including pain due to OA and RA. A 1996 analysis of opioid therapy for nonmalignant pain concluded that there is a place for these drugs in such pain (Portenoy, 1996). The American Pain Society (APS) and the American Academy of Pain Medicine (AAPM) issued a policy statement that it is appropriate to use opioids in the management of chronic nonmalignant pain when other available management strategies have produced inadequate pain relief (APS & AAPM, 1996).

Opioids should be used for patients with OA and RA when other medications and nonpharmacologic interventions produce inadequate pain relief and the patient's quality of life is affected by the pain. Morphine, oxycodone, hydrocodone, or other mu agonist opioids, as a single agent or combined with an NSAID or with acetaminophen, should be used for moderate to severe OA or RA pain that has not responded to other treatments.

The use of opioids for chronic nonmalignant pain is both legal and clinically important. This is documented by the fact that the Federation of State Medical Boards of the United States published model guidelines for the use of controlled

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substances in the treatment of pain including chronic nonmalignant pain in May 1998 (Federation of State Medical Boards, 1998).

Clinicians in traditional rheumatology practice have avoided using opioids in most cases because of concerns about adverse effects. Recent studies have greatly increased the understanding of addiction, physical dependence, tolerance, and other adverse opioid effects.

Addiction, Physical Dependence, and Tolerance

Opioid addiction, dependence, and tolerance are important concepts that are not well understood by many clinicians or by the general public, leading to fear of using opioids that results in many patients suffering unnecessarily. A consensus statement by APS, AAPM, and the American Society of Addiction Medicine (ASAM) defines *addiction* as follows:

Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by one or more of the following behaviors: impaired control over drug use, compulsive use, continued use despite harm, and craving (2001, p. 2).

The prevalence of addiction among patients with pain who do not have a previously existing substance abuse disorder is low.

Weissman and Haddox (1989) noted that patients who are given doses of opioids that are inadequate to relieve their pain or whose opioid dose is discontinued abruptly or tapered too rapidly may develop characteristics that resemble addiction, which they termed iatrogenic "pseudoaddiction." Patients are often quite knowledgeable about their medications and the doses that have worked in the past. Requests for these specific medications and doses should not be interpreted as necessarily indicating drug-seeking behavior.

As in the general population, the small number of patients who do have problems with substance abuse require individualized treatment to provide competent and humane management of their pain. Treatment of such patients is complex and is not covered in this guideline; consultation from appropriate interdisciplinary specialists should be considered.

Physical dependence is a state of adaptation that is manifested by a medication class specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the medication, and/or administration of an antagonist (APS et al., 2001). Physical dependence occurs in nearly all patients who take opioids on a regular schedule for a week or more. These patients can be tapered off opioids, if indicated, in the same way that patients taking steroids or beta-sympatholytic agents are tapered off their medications when they are no longer needed (Hare & Lipman, 1990). When opioids are administered for more than 5–7 days, the dose should be tapered to avoid the physiologic symptoms of withdrawal, which include dysphoria, nasal congestion,

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diarrhea, nausea and vomiting, sweating, and seizures. Physical dependence is neither a risk factor for addiction nor a difficult clinical problem.

Tolerance is a state of adaptation in which exposure to a medication induces changes that result in a diminution of one or more of the medication's effects over time (APS et al., 2001). The phenomenon of tolerance to opioids has three distinct components: (1) analgesia, (2) sedative, cognitive, and psychomotor effects, and (3) opioid-induced constipation (Lipman & Jackson, 2002). Tolerance to analgesia is uncommon once pain relief has been achieved and there is no progression of disease. Some tolerance to sedative, cognitive, and psychomotor effects of opioids occurs typically after about a week of regularly scheduled therapy. Tolerance to opioid-induced constipation does not occur.

Tolerance to opioid analgesia often appears to occur during the first days to weeks of therapy. This may be a dose finding period rather than tolerance. After a dose that provides relief is found and maintained for a week, it is rare for patients to require escalating doses unless there is increased or new pathology, treatment nonadherence, medication interaction, or some other concurrent factor. The need to escalate doses for these reasons has been termed "pseudotolerance" (Pappagallo & Heinberg, 1997).

Tolerance to cognitive, sedative, and psychomotor effects is normal, and patients who start on opioids or whose opioid dose is increased should be counseled that the drowsiness and impaired coordination will improve within a week. Many patients are able to operate motor vehicles safely after a week of regularly scheduled opioid dosing (Vainio, Ollila, Matikainen, Rosenberg, & Kalso, 1995). If the dose is increased, patients should be advised to avoid driving or operating machinery until they have developed tolerance to any increased opioid effects that could make those activities dangerous.

Mu opioid receptors in the colon are activated by systemic opioids, which reduces peristalsis. Thus, constipation should be anticipated and promptly treated with a stimulating laxative such as senna or bisacodyl, and not with a stool softener alone.

Effectiveness and Use of Opioids

Clinical research and practice have demonstrated consistently that most people respond similarly to equianalgesic doses of different mu agonist opioids (e.g., morphine, oxycodone, hydromorphone). However, the recent cloning of multiple mu opioid receptors (Pasternak, 2001) supports the observation that some individuals may respond more to one mu agonist than another. Failure of a person to respond to one opioid is not a basis to conclude that the pain is opioid-resistant. Other opioids may be effective.

Few controlled studies of opioid analgesics have been done in OA and even fewer in RA pain management. However, studies that have been completed clearly indicate the effectiveness and clinical usefulness of these drugs in treating moderate to

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severe arthritis pain. Furthermore, decades of clinical experience and studies conducted in patients with chronic nonmalignant pain due to a variety of causes have demonstrated clearly the usefulness of opioids in the management of a variety of chronic nonmalignant pain types.

There is some evidence of a positive risk-to-benefit ratio in the use of certain opioids for people with moderate to severe pain from OA and RA. (See Chapter II, "Table of Evidence for Opioids in Arthritis Pain.") Opioids studied for OA and RA pain are the mu agonists codeine and oxycodone, the weak opioid propoxyphene, and the mixed agonist-antagonist pentazocine.

RCTs of codeine have produced mixed results in both OA and RA pain, and adverse effects frequently cause patients to stop taking codeine. RCT data show that codeine alone is no more effective than placebo in OA pain; codeine plus NSAID was marginally more effective than NSAID alone. Codeine plus acetaminophen was no different from propoxyphene plus acetaminophen in effects produced. In RA pain, codeine—with and without acetaminophen—was more effective than placebo, and codeine alone was more effective than propoxyphene. Other mu agonist opioids have not been studied in a systematic manner in RA pain.

Evidence supports the use of oxycodone for moderate to severe pain that has not responded to other treatments. Low-dose oxycodone has been shown to be effective in RCTs for OA pain both as immediate-release and controlled-release tablets. Controlled-release tablets produce fewer side effects than the immediate-release dosage forms. Oxycodone (10 mg) controlled-release tablets produced 19%–53% improvement over placebo with no significant increase in side effects. Oxycodone (20 mg) controlled-release tablets had greater efficacy for analgesia than the 10-mg tablets, but nausea, constipation, and drowsiness also increased (Roth et al., 2000). Clinical experience suggests that other mu agonist opioids (e.g., morphine, hydromorphone, methadone) also might be effective in treating OA and RA pain.

Opioids should be used for patients with OA and RA when other medications and nonpharmacologic interventions produce inadequate pain relief and the patient's quality of life is affected by the pain.

Although there is some evidence of the efficacy of codeine in RA pain, this is not a good choice of opioid because of its high incidence of adverse side effects. Other mu agonist opioids such as oxycodone, morphine, hydromorphone, and methadone, have not been studied in RA pain. However, these opioids have been shown to be better analgesics than codeine in other chronic non-malignant pain models and may be better choices than codeine in treating RA pain.

Propoxyphene alone produced no more analgesia than placebo in either OA or RA pain. Propoxyphene produced little to no additional analgesia when compared to propoxyphene-acetaminophen combinations in both OA and RA.

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Propoxyphene alone produced variable results when compared to NSAID alone in OA pain (Brooks, Dougan, Mugford, & Meffin, 1982). Evidence does not support the use of propoxyphene in OA or RA pain. The use of codeine and propoxyphene should be avoided because of their side effects and limited analgesic effectiveness.

Pentazocine has been shown to be more effective than propoxyphene and less effective than aspirin in RA pain. There is no evidence to support use of this or other mixed agonist-antagonist opioids (i.e., pentazocine, butorphanol, and nalbuphine) in OA pain management.

Extensive experience and evidence in the management of chronic malignant pain supports the use of long-acting opioids to improve patient adherence, minimize medication level peaks and valleys, and minimize side effects. These advantages also appear to apply to the use of long-acting opioids in the management of arthritis pain, but the cost-effectiveness of the advantages has not been shown.

Table 17 presents dosing data for opioids commonly used in treatment of acute pain and cancer pain. As described previously, few of these have been studied in patients with arthritic pain.

Opioid Dosing

There is no standardized correct dose of opioid for any given patient or indication. Titration to response is the only consistently useful way to determine the optimal dose. Likewise there is no predetermined maximum oral dose for the pure mu agonist opioids. Doses should be increased as necessary for pain relief within the bounds of side effects acceptable to the patient. Starting doses for moderate to severe pain should be conservative, especially in older and renally impaired people. Doses may be increased as soon as steady state serum levels are achieved. For morphine and oxycodone, which have half-lives of about 2 hours, steady state levels are achieved in about 10 hours. Therefore, doses may be increased daily without concern for too rapid escalation causing accumulative toxicity. The inherently long-acting opioids methadone and levorphanol have much longer half-lives and must be titrated more slowly and carefully. Opioids differ in potency because of their specific properties, but can be made equivalent or equianalgesic by changes in dosage or routes of administration (APS, 1999; Jacox et al., 1994). Table 18 provides a list of opioids, their cost, and clinically significant adverse effects.

For patients taking regularly scheduled opioids for a week or more, dose increases should be 50% of the previous dose. This percentage applies no matter what the previous dose. A common reason for incorrectly assuming that pain is not opioid responsive is using dose increases that are too small. Once patients' pain is well controlled for a few weeks, it is not uncommon to be able to reduce

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Table 17. Usual Starting Doses for Opioid Analgesics in Opioid Naïve Adults ≥ 50 kg Body Weight*

Medication (Trade Name)	Usual Starting Oral Dose for Moderate to Severe Pain ^b	Special Considerations
Short-Acting Opioid Agonists Codeine	Not recommended because of adverse side effects common even at minimally effective analgesic doses.	Short-acting opioid agonist
Hydrocodone and acetaminophen ^c (Lorcet, Lortab, Vicodin)	5-10 mg q.i.d. hydrocodone ^b	Available only in combination with acetaminophen, aspirin, or ibuprofen
Hydrocodone and ibuprofen ^c (Vicoprofen)		More likely than most other opioids to cause side effects
Hydrocodone and aspirin ^c (Lortab ASA)		associated with histamine release
Hydromorphone ^d (Dilaudid, others)	2-3 mg q.i.d.	Short-acting opioid agonist
Meperidine (Demoral, others)	Not recommended because of potential CNS side effects.	Very short-acting opioid agonist Risk of seizures when used for > 2 days
Morphine ^d (MSIR, Duramorph, Roxanol, others)	7.5-15 mg q.i.d.	Short-acting opioid agonist
Oxycodone (Roxicodone, Oxycot)	5-10 mg q.i.d.	Short-acting opioid agonist
Long-Acting Opioid Agonists Morphine Controlled-Release (MS Contin, Duramorph SR) (Kadian)	30 mg q 12h 30 mg q 8h	Controlled-release Opioid agonist
Oxycodone Hydrochloride-ER (OxyContin)	10-20 mg q 12 h	Controlled-release opioid agonist Tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin leads to rapid release and absorption of a potentially fatal dose of oxycodone.
Fentanyl, Transdermal (Duragesic)	25 mcg (0.025mg)/h (one transdermal system for 72h)	Controlled-release opioid agonist Correct patch application procedure must be followed. Avoid direct exposure of application site to heat.

*Caution: Recommended doses do not apply to adult patients with body weight less than 50 kg.

^bDoses computed by using doses that are equianalgesic with dose of oxycodone shown to be effective in moderate to severe OA pain.^cThis dosage is for hydrocodone only.^dCaution: These products contain aspirin, acetaminophen, or ibuprofen. Total daily doses of acetaminophen that exceed 5 gm may be associated with severe hepatic toxicity. Aspirin is contraindicated in children in the presence of fever or other viral disease, because of its association with Reye's Syndrome.^eCaution: Recommended doses do not apply to patients with renal or hepatic insufficiency or other conditions affecting medication metabolism and kinetics.

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Table 18. Clinically Significant Adverse Effects and Costs of Opioids in Adults

Medication (Proprietary or Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b		Clinically Significant Frequent Adverse Events ^c	Special Considerations
		Lowest	Highest		
Codeine				GI, CNS	Not recommended for use Adverse side effects common even at minimally effective analgesic doses, constipation, drowsiness and nausea
Fentanyl, Transdermal (Duragesic)	25 mcg (0.025 mg)/ hour (one transdermal system for 72 hours)		\$140	R, GI, CV, CNS	Should be prescribed and monitored by persons knowledgeable in the continuous administration of potent opioid analgesics and in the management of hypoventilation. Correct patch application must be followed. Avoid direct exposure of application site to heat. ⇒ Not recommended for treatment of acute pain, may cause severe hypoventilation.
Hydrocodone and acetamin- ophen (Lorab, Lortab, Vicodin)	30 mg ^d	\$68	\$125	CV, CNS	May have decreased BP, fast heartbeat, increased sweating, redness or flushing of face, wheezing or troubled breathing; dizziness & lightheadedness—especially in ambulatory patients; drowsiness; orthotic hypotension—especially in ambulatory patients; unusual tiredness or weakness
Hydrocodone and ibuprofen (Vicoprofen)		\$121	\$131		
Hydrocodone and aspirin (Lortab ASA)		\$26	\$41		
Hydromorphone (Dilaudid, others)	10 mg	\$42	\$65	CV, CNS, GI	Dizziness and lightheadedness—especially in ambulatory patients; drowsiness; orthotic hypotension commonly occurs in ambulatory patients; loss of appetite can occur; unusual tiredness or weakness

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Table 18. (cont.) Clinically Significant Adverse Effects and Costs of Opioids in Adults

Medication (Proprietary or Trade Name)	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b		Clinically Significant Frequent Adverse Events ^c	Special Considerations
		Lowest	Highest		
Meperidine (Demerol, others)				CV, CNS, GI, HEM	Not recommended for use More likely than most other opioids to cause side effects associated with histamine release, convulsions, or constipation. Precautions: May increase effects of anti-coagulants. Contraindicated when MAO inhibitor taken in past 14–21 days; serious sometimes fatal reactions
Morphine ^d (Duramorph, MSIR, Roxanol, others)	45 mg	\$18	\$31	CV, CNS, GI	May have decreased BP, fast heartbeat, increased sweating, redness or flushing of face, wheezing or troubled breathing; hypotension; unusual tiredness or weakness
Morphine Controlled-Release (Kadian, MS Contin, OramorphSR, Roxanol, Stages, others)	60–90 mg	\$99	\$179	CV, CNS, GI	
Oxycodone (Roxicodone, Oxylin)	30 mg	\$63	\$69	CV, CNS, GI	Dizziness and lightheadedness—especially ambulatory patients; drowsiness; orthotic hypotension
Oxycodone Hydrochloride—ER (OxyContin)	30 mg	\$112–\$113		CV, CNS, GI	Tablets are to be swallowed whole and are not to be broken, chewed, or crushed. Taking broken, chewed, or crushed OxyContin tablets leads to rapid release and absorption of a potentially fatal dose of oxycodone.

^aFor medications with a range of therapeutic dosages, the midpoint between the lowest dose and highest dose was used to represent an average 24-hour dose (July 2001).

^bAverage wholesale price, First Data Bank Price Check PC. All costs for lowest and highest price per unit were calculated based on the average 24-hour dosage and rounded to the nearest dollar.

^cUSP DI Vol. I, Drug Information for the Health Care Professional, 2001, ISBN 1-56363-331-0

^dThis dose is for hydrocodone only.

Key: The following symbols mean that an adverse effect occurs frequently (3%–9%) with the specific drug:
BP = blood pressure, CNS = central nervous system, CV = cardiovascular, GI = gastrointestinal, HEM = hematologic, R = renal
— = Major clinical significance

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the dose by 20%–25% because pain-induced anxiety lessens after pain control is achieved.

Oxycodone has been studied more extensively in the management of OA pain than other mu agonist opioids. It is reasonable to extrapolate the oxycodone results to other drugs in the class using well-documented equianalgesia doses. Opioids such as morphine, oxycodone, hydromorphone, and methadone are preferable to codeine and meperidine for analgesia in arthritis pain. To define appropriate opioid doses for arthritis pain, we extrapolated from the evidence on oxycodone efficacy in OA pain (the best evidence available on opioids for arthritis pain) and calculated doses of other commonly used opioids based on well-documented equianalgesic doses. The limited study data on effective doses of opioids for OA pain demonstrate efficacy at relatively low doses. Both immediate-release and controlled-release forms have been effective.

There is no published evidence on dosing of hydrocodone per se. Because hydrocodone is a schedule III controlled substance (not schedule II as are morphine, hydromorphone, and oxycodone), it is one of the most commonly used opioids in managing all types of moderate to severe pain. It is available commercially only in combination with acetaminophen or aspirin (e.g., Lortabs, Vicodin). Dosing and effectiveness of hydrocodone in a broad range of painful disorders appear to be the same as that of oxycodone.

Methadone is an effective, long-acting opioid. The dose requirements and kinetics are highly variable, especially before steady state serum levels are achieved, which may require up to 10 days even with regularly scheduled dosing. Therefore, dose equivalencies for this opioid are not listed.

Although the opioids listed in Table 18 have comparable activity in most patients, some respond better to one of these medications than another. Therefore, if a patient does not appear to obtain reasonable analgesia despite rapidly increasing doses of one opioid, another should be tried.

Concurrent use of NSAIDs provides an opioid dose sparing effect. The oral route is the preferred method of administration for nearly all arthritis analgesics. Transdermal administration also can be considered for patients who have difficulty taking oral medications or who have adherence difficulties, which favor a longer-acting dosage form. The commercially available fentanyl transdermal patch (Duragesic) provides 48–72 hours of analgesia. This patch has not been studied in arthritis pain management. The smallest patch currently available delivers 25 mcg per hour, which, according to the FDA-approved dose equivalency, is equivalent to about 50–160 mg of morphine per day (12.5–40 mg four times a day). A 12.5 mcg per hour patch currently under development is a dosage form that might provide more appropriate dosing for arthritis pain management.

Opioids are potent medications that can be highly toxic, especially when first taken. Clinicians should educate patients about the importance of storing

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opioids in places where unauthorized persons do not have access to the medications. Because controlled-release dosage forms usually contain greater quantities of opioid per tablet, capsule, or patch than do immediate-release dosage forms, one controlled-release dosage form is potentially more toxic than one immediate-release form. This risk mandates appropriate control of the medications but should not limit their clinical use when indicated.

Tramadol

Tramadol is an analgesic that binds weakly to mu opioid receptors and inhibits the reuptake of serotonin and norepinephrine. Neither of these effects alone can account for the medication's analgesic efficacy, which appears to result from an additive effect between the two mechanisms (Roth, 1998). Tramadol is an effective analgesic for moderate pain (4-6 on a scale of 0-10). It is not a controlled substance, and reports of abuse of tramadol are rare. It is not an antiinflammatory agent. Tramadol can be dose sparing for NSAIDs, and a combination of tramadol with an NSAID can be clinically useful if a maximum antiinflammatory NSAID dose is inadequate to provide pain relief. A 1999 study showed that combination therapy of tramadol with the NSAID naproxen allowed the use of lower doses of naproxen for control of symptoms in OA patients (Schnitzer et al., 1999).

Tramadol may be used alone or in combination with acetaminophen or NSAIDs for therapy at any time during the treatment of a patient with OA when NSAIDs alone produce inadequate pain relief.

Tramadol is available in 50 mg tablets, and up to 400 mg per day can be administered. Patients with chronic renal insufficiency or who are older than 60 years of age should receive doses no higher than 250-300 mg per day (Katz, 1996). The medication cannot be given with monoamine oxidase (MAO) inhibitors. There are adverse effects associated with the use of tramadol: nausea, vomiting, and dysphoric reactions appear to be directly related to the initial starting dose. Because there is evidence that slow titration decreases the incidence of these effects, therapy usually should be started at 50 mg once daily and increased slowly (Petroni, Kamin, & Olson, 1999). For some sensitive and older people, it may be necessary to initiate therapy at 25 mg (1/2 a tablet). Seizure is an uncommon adverse effect that may be dose related (Jick, Derby, Vasilakis, & Fife, 1998). The incidence of seizures appears to be increased in patients who are rapidly titrated to high doses and in patients with systemic lupus erythematosus. Table 19 charts dosage, cost, and special considerations for administering tramadol.

Pharmacotherapy for Neuropathic Pain

Pharmacotherapy for neuropathic pain is not definitive. Numerous classes of medications have been studied with varying claims of efficacy, but no one class is consistently efficacious for neuropathic pain. Tricyclic antidepressants have been

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Table 19. Dosage, Clinically Significant Adverse Effects, and Cost of Tramadol in Adults

Medication (Trade name)	Usual Starting Dosage for Moderate Pain	24-Hour Average Dosage ^a	Cost for 30-Day Supply ^b	Clinically Significant Frequent Adverse Events ^c	Special Considerations
Tramadol (Ultram)	50 mg q.d. up to 400 mg q.d.	225 mg	\$115	CV, CNS, R, HY, O	Binds weakly to mu- opioid receptors—not an antiinflammatory agent ⇒ Should not be used when following condi- tions present: acute intoxication with alco- hol, hypnotics, central- ly-acting analgesics, opioids or psychotropic drugs due to risk of res- piratory depression Use with great caution in patients taking MAO inhibitors

^aFor medications with a range of therapeutic dosages, the midpoint between the lowest dose and highest dose was used to represent an average 24-hour dose.

^bAverage wholesale price, First Data Bank Pricer Check PC, July 2001

^cLSP DI Vol 1, Drug Information for the Health Care Professionals, 2000, ISBN 1-56363-331-0

Key: The following symbols mean that an adverse effect occurs frequently (3-9%) with the specific drug:

CNS = central nervous system, CV = cardiovascular, HY = hypersensitivity, R = renal, O = other

⇒ Major clinical significance

shown to be the most effective pharmacological monotherapy for neuropathic pain (Sindrup & Jensen, 1999). Tricyclic antidepressants act by inhibiting reuptake of norepinephrine and serotonin, which are neurohumoral transmitters needed for normal nociceptive neuron function. Desipramine has the lowest incidence of adverse effects and optimal pharmacokinetics, making it a tricyclic agent of choice for this purpose (Lipman, 1996). Dosing normally starts at 25 mg at bedtime increased at 3-day intervals to a daily dose of 100 mg.

When treatment with a tricyclic antidepressant is not adequate after a 2-week trial, an anticonvulsant is added. Gabapentin is the best tolerated anticonvulsant studied for neuropathic pain. Dosing typically starts at 100 mg three times a day, increased every few days by 300 mg per day. Most patients who respond do so at total daily doses of 900-1,800 mg. Clinical experience suggests a dose response that may justify higher doses in patients who do not respond adequately to

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1,800 mg per day. Topical lidocaine (Lidoderm Patch) also is effective in managing neuropathic pain. Anticonvulsants and local anesthetics stabilize the neuronal membranes.

Physical therapy and behavioral interventions also may be needed to manage neuropathic pain. Referral to an interdisciplinary pain program may be indicated for patients who do not respond to these primary treatments.

Dietary Supplements and Nutrition

Recommendations in This Section*

17. Adults with OA should be encouraged to take 1,500 mg of oral glucosamine sulfate daily. (A)

18. People with arthritis should be advised to maintain an ideal body weight and adhere to a balanced diet containing adequate amounts of protein, fat, vitamins, and minerals. Adults should lose weight if their body mass index (BMI) is greater than 30, and follow a weight management program. Children should lose weight if their BMI is greater than the 95th percentile for children of the same age and gender. (B)

*Please note: Recommendations appear in bold type as they are discussed in the text. See Chapter II for an explanation of the strength of the evidence supporting the recommendations.

Biologic Agents

There has been considerable consumer interest in the application of "complementary or alternative medicine (CAM)," including biologic agents, to the treatment of OA and RA. These therapies have several things in common: The research is associated with a high placebo rate, they are not FDA regulated, there are few long-term outcome studies, and there is a low risk of complications or side effects.

Glucosamine sulfate. Oral glucosamine sulfate is derived from chitin or is synthesized, and product standards are inconsistent. There is some evidence that glucosamine sulfate is a chondroprotective agent that stimulates the production of cartilage matrix and provides nonspecific protection as an antioxidant against chemical damage. Results of most clinical trials in people with OA, primarily of weight-bearing joints, demonstrate benefits up to 8 weeks in reduced pain and increased function after IM or oral treatment (Moore, Tramer, Carroll, Wiffen, & McQuay, 1998). Adverse effects over this short period have been minimal and mainly GI. Only the oral form is available in the United States, and it has a fairly low first-pass bioavailability of 26%. The most frequently used oral dosing is 500 mg of glucosamine sulfate three times a day.

In a recently reported double-blind, placebo-controlled RCT of people with knee OA, those in the experimental group were given 1,500 mg of oral glucosamine sulphate daily for 3 years (Reginster et al., 2001). People who received

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glucosamine had significantly less joint-space narrowing as measured by radiograph, and 20%–25% improvement in pain and physical functioning as measured by the Western Ontario and McMaster Universities (WOMAC) OA Index. There were no differences in adverse effects or study withdrawal between the two groups. Therefore, adults with OA should be encouraged to take 1,500 mg of oral glucosamine sulfate daily.

Chondroitin 4-sulfate. Chondroitin 4-sulfate is a glycosaminoglycan consisting of repeated disaccharide units. It may stimulate production of the cartilage matrix and have antiinflammatory activity. Because of its high molecular weight it is not absorbed well from the GI tract (10%). A small number of clinical trials have demonstrated improvement in pain and function with daily oral doses of chondroitin 4-sulfate of 1,200 mg. In a double-blind RCT, chondroitin sulfate was as effective as the NSAID diclofenac in decreasing pain (Morreale, Manopulo, Galati, Boccancera, Saponzi, & Bocchi, 1996). Pain relief from chondroitin 4-sulfate lasted 3 months after cessation of treatment, whereas pain increased soon after stopping treatment with diclofenac.

There are preparations containing both glucosamine and chondroitin 4-sulfate, but standardization of potency of these "nutritional supplements" is not required and potencies are known to vary. The effects of treatment occur within weeks (glucosamine) to months (chondroitin 4-sulfate) after initiating treatment. No long-term consequences (in years) have been studied for chondroitin 4-sulfate with regard to effectiveness, disease-modifying activity, or adverse effects.

S-adenosylmethionine. S-adenosylmethionine (S-AdMe) is a natural compound that plays a role in various metabolic processes and may be both antiinflammatory and chondroprotective. Several RCTs have compared S-AdMe with placebo, naproxen, indocin, piroxicam, and ibuprofen in OA of the knee, hip, and spine (Maccagno, Di Giorgio, Caston, & Sagasta, 1987; Muller-Fassbender, 1987; Vetter, 1987). Pain reductions were equivalent to NSAIDs although slower in onset. S-AdMe has been used for up to 2 years with continued benefit. There is no standard dose, and the potency of products on the market varies.

Until there have been longer-term studies and more standardization of dosages with other dietary supplements, no recommendations can be made about their use.

Nutrition

The role of nutrition in reducing or eliminating pain in people with arthritis is not well understood. Studies have shown that nutrition has an impact on inflammatory diseases that results in an improvement in clinical symptoms in people with rheumatic diseases (Kremer, 1991). Regulation of the oxygenation of arachadonic acid (AA) for eicosanoid formation requires antioxidants, examples of which are vitamins E, C, and A as well as selenium-, copper-, zinc-, and iron-containing metalloenzymes. These pro- and antioxidative nutrients may

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have an impact on inflammation in rheumatic disease. Other nutrients, such as fats and oils, alcohol, and flavinoids, display antiinflammatory or proinflammatory effects.

Fish and plant oils. The ingestion of fish oils, which contain omega-3 polyunsaturated fatty acids, causes AA to be replaced by eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in cell membranes. This replacement leads to a decrease in the production of the inflammatory metabolites of AA, which may decrease inflammation and joint pain.

There is consistent evidence from double-blind, placebo-controlled RCTs that the intake of dietary n-3 polyunsaturated fatty acids, supplied as fish oil, reduces morning stiffness and joint tenderness in RA (Cleland, French, Betts, Murphy, & Elliott, 1988).

The dietary supplement is 3–6 g of omega-3 fatty acids taken daily for 12 weeks or longer (Kremer, 2000). Some people who take fish oil are able to discontinue NSAIDs without experiencing a disease flare (Kremer et al., 1995). In other studies, fish oil related improvement in tender and swollen joints were more pronounced in a vegetarian group (Adam & Kramer, 1995). The clinical usefulness of fish oils or plant-derived fatty acid analogues in the treatment of RA is not clear because of the uncertainty of how much to consume, which components of the oils are most effective, the duration of therapy, and other factors (Kremer, 1991). Fish oil has not been shown to benefit patients with OA (Nordstrom, Honkanen, Nasu, Antila, Friman, & Kontinen, 1995).

Fatty acid supplements that were studied in patients with RA include inert paraffin wax, corn oil, olive oil, primrose oil, and borage oil (Kjeldsen-Kragh, 1999; Kremer, 2000; Kremer et al., 1990; Sperling et al., 1987). Olive oil, which has a high n-9 fatty acid content and antioxidant properties, did not reduce morning stiffness or pain as well as fish oil supplements (Linos et al., 1999). Use of these fats and oils in clinical studies of patients with RA has not had a significant impact on clinical outcomes (Jantti, Seppala, Vapaatalo, & Isomaki, 1989).

Fasting and vegetarian diets. Fasting was shown in several studies to reduce pain and stiffness in some people with RA, but most relapse with the reintroduction of food (Hafstrom, Ringertz, Gyllenhammar, Palmblad, & Hamns-Ringdahl, 1988). Reduction of joint inflammation and pain was sustained if a vegetarian diet was followed (Kjeldsen-Kragh et al., 1991), and the number of tender joints and duration of morning stiffness was reduced by fasting followed by a vegetarian diet for 1 year (Haugen, Kjeldsen-Kragh, Bjerve, Hostmark, & Forre, 1994). It has been suggested that the combined reduction in animal fats, removal of possible food allergens, and the inclusion of more antioxidant vitamins may account for the improvement. Some patients with RA may benefit from a fasting period (7–10 days maximum) followed by a vegetarian diet. The long-term benefits of this approach remain to be determined.

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Food sensitivities. Food allergies may influence rheumatic disease because foods can evoke immune responses and they can cause immunologically mediated symptoms. Studies of the effectiveness of food elimination are anecdotal, incompletely blinded and uncontrolled and/or have small sample sizes. They have not identified particular food(s) that consistently appear to be problematic in people with RA. More well-controlled studies are needed to define who may benefit from what diets, under which circumstances, and to what extent.

Supplements and other diets. Limited evidence is available about the effectiveness of specific diets or supplements in managing pain in people with arthritis. Some studies showed positive results with uncooked vegan diets, individual vitamin and/or mineral supplements (e.g., copper, zinc, vitamins B, C, E), or other products such as Brewer's yeast, garlic, cod liver oil, bromelain (in pineapple and vinegar), and ginger (Delafuente, 1991; Panush, 1993; Srivastava & Mustafa, 1992). Some diets and supplements may have adverse health consequences if followed for prolonged periods of time and/or in high doses (Wolman, 1987). No "arthritis diet" has been studied adequately and no recommendations can be made for such diet prescription or for other diets such as avoidance of "nightshade foods" (foods from the Solanaceae family such as tomatoes) to reduce arthritis symptoms (Childers & Margolis, 1993).

Fish oil supplements and a vegetarian diet may reduce pain in some patients with RA. Self-imposed elimination diets should be avoided and suspected food intolerances/allergies tested only under close clinical supervision. Nutrient megadosing is inadvisable, although dietary supplements of calcium, vitamin D, vitamin E, zinc, and folic acid may be needed if dietary intake is inadequate (Stone, Duabe, Dudson, & Wallace, 1997).

Obesity

Obesity (BMI greater than 30) was shown in numerous studies to be associated with an increased prevalence of hip and knee OA. Weight loss reduces the risk for symptomatic knee OA in women (Felson & Chaisson, 1997). It is not known whether weight loss slows the progression of existing OA, but BMI less than 25 generally reduces the risk of disease and even small amounts of weight reduction may have favorable effects (Felson & Chaisson). Thus, individuals who are chronically overweight should lower their risk for knee OA through weight loss. People with arthritis should be advised to maintain an ideal body weight and adhere to a balanced diet containing adequate amounts of protein, fat, vitamins, and minerals. They should lose weight if their BMI is greater than 30, and follow a weight management program. Children should lose weight if their BMI is greater than the 95th percentile for children of the same age and gender.

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Exercise and Physical Modalities in the Management of Arthritis Pain

Recommendations in This Section*

19. All individuals should be encouraged and supported to participate in the minimum level of physical activity recommended by the U.S. Surgeon General (1996). Participate in at least 30 minutes of moderate physical activity on most days of the week. (B)
20. People with OA, RA, or JCA who have difficulty in maintaining minimum levels of physical activity should be referred to appropriate conditioning exercise opportunities in the community and their progress followed routinely by the healthcare team. When necessary to prepare an individual for successful participation in a community-based or self-directed exercise program, referral should be made for physical therapy and/or occupational therapy to evaluate and reduce impairments in range of motion, flexibility, strength, and endurance and instruct in joint protection strategies. (B)

*Please note: Recommendations appear in bold type as they are discussed in the text. See Chapter II for an explanation of the strength of the evidence supporting the recommendations.

Most individuals seek care when pain interferes with function and social roles; thus, clinical care focuses on the resolution of the immediate crisis and pain reduction. Because arthritis is a chronic, often progressive condition, clinicians should be knowledgeable about the potential trajectory of the disease and long-range outcomes. Exercise and the use of physical modalities are important components of a comprehensive management program for people with OA or RA.

Understanding of the role that exercise plays in managing arthritis has changed over time. The traditional recommendations were to rest, avoid vigorous activities, and perform only range-of-motion and isometric exercises. This approach assumed that repetitive motion, weight-bearing, or vigorous exercise would damage tissues and increase fatigue. Protecting joints from pathologic stress and increasing rest during periods of disease activity are important components of good care. For the person with arthritis, however, the consequences of unnecessary and prolonged inactivity add to the problems of pain, stiffness, loss of motion, weakness, functional limitations, poor health, and disability.

Arthritis can create serious health problems in ways other than the direct consequences of disease and side effects of therapy. Arthritis is the primary cause for limitation in physical activity in adults. In one study, three-quarters of older adults reported limitation in physical activity and more than one-third were limited in activities of daily living (ADLs) due to arthritis (Yelin, 1992). In another, people with RA reported that one of the first adaptations they made was to

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give up leisure and recreational activities (Yelin, Lubeck, Holman, & Epstein, 1987), which are a primary source of physical activity for adults. People with longstanding or severe OA tend to be de-conditioned and at increased risk for cardiovascular disease. In addition to the many health risks of inactivity, inactivity produces many of the same signs and symptoms traditionally attributed to the arthritis disease process and subsequent disability, namely muscle weakness and atrophy, fatigue, stiffness, decreased flexibility, cardiovascular deficits, incoordination, osteoporosis, depression, and lowered pain threshold.

Adequate levels of physical activity are essential to maintain general health and reduce the risk of inactivity-related diseases. The U.S. Department of Health & Human Services (1996) recommended that all adults maintain at least a minimum level of physical activity. Recommendations for physical activity for health (Table 20) are appropriate for most people with arthritis. They can be used to assess activity status and provide guidance for physical activity for individuals who are currently sedentary.

Appropriate regular exercise, both therapeutic and self-directed, can improve deficits related to inactivity as well as reduce pain, fatigue, and depression. Therapeutic exercise is prescribed for the person with arthritis to (a) reduce impairment (e.g., range of motion/flexibility, strength, muscular function, pain, fatigue); (b) maintain or improve function (e.g., ADLs, locomotion, balance); and (c) prepare for safe participation in adequate levels of regular exercise or physical activity needed for cardiovascular health and general fitness.

Exercise performed at conditioning levels can improve flexibility, strength, endurance, function, cardiovascular fitness, and general health status with no aggravation of pain or symptoms (Minor, 1991; Van Den Ende, Vliet Vlieland, Munneke, & Haze, 2000). Furthermore, regular joint motion and weight bearing appear to protect cartilage and bone from atrophy (Houlbrooke, Vause, & Merrilees, 1990). Regular exercise of moderate intensity can raise the pain threshold, improve energy level, lessen depression, and improve physical self-concept and self-efficacy (Harkcom, Lampman, Banwell, & Castor, 1985; Kovar et al., 1992; Stenstrom, 1994). Limited weight-bearing activities (e.g., aquatic exercise, stationary bicycling) and weight-bearing exercise (e.g., walking, low-impact aerobic dancing) are safe for many people with symptomatic weight-bearing joints. Tables 21 and 22 present exercise recommendations for cardiovascular and muscular fitness.

Exercise Types

Exercise is categorized into three main types: (a) flexibility and range-of-motion exercise, (b) muscle-conditioning exercise, and (c) aerobic exercise. Each type has a place in the exercise regimen of a person with arthritis.

Range-of-motion and flexibility exercise. Flexibility exercises, also known as range-of-motion and stretching exercises, increase or maintain flexibility and

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Table 20. Recommendations for Physical Activity for Health

Purpose	Establish a pattern of regular physical activity to promote general health
Exercise mode	Perform activities that involve large muscle groups, entire body if possible, in dynamic, repetitive motion. Examples: walk, swim, dance, bicycle, row, aquatic exercise, calisthenics, household, and garden tasks
Intensity	Low to moderate intensity: 50%–75% of age-predicted heart rate; rating of perceived exertion = 3–5; talk test = able to converse comfortably
Duration	Accumulation of 30 minutes per exercise day
Frequency	Three to four times a week for moderate intensity; daily for low intensity

motion in muscles, tendons, ligaments, and joints and are the basics of any exercise program. Flexibility is necessary for good posture and strength, for comfortable movement during daily activities, and to reduce the risk of sprains and strains. It takes less energy and causes less fatigue to move when the body is flexible and moves easily. In arthritis, active and active/self-assisted exercise can relieve stiffness, increase or maintain joint motion, and increase length and elasticity in muscle and periarticular tissues. Gentle range-of-motion exercise performed in the evening can significantly reduce morning stiffness for people with RA (Byers, 1985). An exercise program of active exercise and relaxation (e.g., the ROM Dance program) has produced significant improvement in function and pain (Van Deusen & Harlowe, 1987).

Flexibility exercises should be done gently and smoothly, 3–10 times each, usually every day. Flexibility exercises also should be performed before and after any more vigorous type of exercise or daily tasks. A person who has not exercised regularly in some time, or who has pain, stiffness, or weakness that interferes with his or her daily activities should begin an exercise program by building a routine of 15 minutes of flexibility exercises. The person who can do 15 minutes of continuous flexibility exercise will have the motion and endurance needed to add strengthening and endurance exercise.

Muscle conditioning or strengthening exercise. Decreased muscle function (strength, endurance, power) in people with arthritis arises from a number of sources: intra-articular and extra-articular inflammatory disease processes, side effects of medication, disuse atrophy, reflex inhibition in response to pain and joint effusion, impaired proprioception, and loss of mechanical integrity around the joint. Muscle conditioning programs can improve strength, endurance, and function without exacerbation of pain or disease activity (Ettinger et al., 1997; van Baar, Assendelft, Dekker, Oostendorp, & Bijlsma, 1999; Van Den Ende et al., 2000).

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Table 21. Recommended Exercises for Cardiovascular Fitness

Purpose	Increase aerobic capacity through improved cardiovascular and muscular performance.
Recommendations	Perform activities that involve large muscle groups, entire body if possible, in dynamic, repetitive motion. Examples: walking, jogging, running, swimming, dancing, bicycling, rowing, and aquatic exercise.
Intensity	Moderate (60%–80% age predicted maximal heart rate); rating of perceived exertion = 3–7; talk test = able to converse comfortably or sing a song.
Duration	Additive or continuous bout of 30–45 minutes of aerobic activity each exercise day.
Frequency	At least three times a week may increase to five times if tolerated at moderate or low levels of exertion.

Table 22. Recommended Exercises for Muscular Fitness

Isometric Exercise	
Purpose	Minimize atrophy; improve tone; maintain/increase static strength and endurance; prepare for dynamic and weight-bearing activity.
Recommendations	Perform at functional joint angles.
Intensity	≤70% one maximal voluntary contraction
Duration	6–10 second contraction
Frequency	5–10 repetitions daily
Precautions	High intensity isometric contraction may decrease local blood flow, increase intra-articular pressure/joint contact force, increase blood pressure. To lessen unwanted effects, exhale during contraction, avoid Valsalva's maneuver, develop force gradually, avoid maximal contraction.
Dynamic Exercise	
Purpose	Maintain/increase dynamic strength and endurance, increase muscle power, improve function, enhance synovial blood flow, improve cartilage and bone health.
Recommendations	Be capable of 8–10 repetitions of motion against gravity before increasing external resistance; perform progressive regimen; perform in pain-free range; use functional activities, movement patterns.
Intensity	Progress to ≤70% one repetition maximum.
Duration	Progress to 8–10 exercises, 8–10 repetitions.
Frequency	Two to three times per week on alternate days
Precautions	Increased force across an unstable or inflamed joint may increase biomechanical stress. To lessen unwanted effects, avoid power gripping and deforming forces on involved hands/wrists. Do not include actively inflamed joints in resistive exercise.

Strengthening exercises, sometimes called resistance exercises, are important for everyone, including people with OA or RA. Joint pain and being sedentary can lead to muscle weakness. Weak muscles are a problem because it takes strong muscles to absorb shock, support joints, and protect from injury. Strong muscles

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also improve endurance and the ability to safely walk, climb stairs, lift, and reach. Strengthening exercises are an important part of an all-around exercise program.

Strengthening exercises make muscles work harder than usual. When muscles are used a little more on a regular basis, they gradually adapt to the extra work by becoming stronger. Strengthening exercises add resistance (extra work) by using the weight of the body, plus extra weights that are held or elastic bands that are stretched. A good strengthening program for people with arthritis consists of overloading muscles just enough to get them to adapt, and not so much they are sore and stiff a day or two after exercises. Strengthening exercises with weights should be done no more than three times a week.

Progressive resistive strength training consistently produces positive results in both pain and function in people with knee OA (Hurley & Scott, 1998; O'Reilly, Muir, & Doherty, 1999). Progressive resistance training in people with RA performed in both supervised and unsupervised settings demonstrated significant increases in strength and function with pain reduction. There is no evidence that resistance training increases pain or disease activity in people with RA (Rall, Meydani, Kehayias, Dawson-Hughes, & Roubenoff, 1996; Komatireddy, Leitch, Cella, Browning, & Minor, 1997). Determination of an appropriate resistance and training schedule, attention to joint protection, monitoring for overexertion, and patient education are important components of a safe and effective program.

Aerobic exercise and physical activity. Aerobic exercise, also known as endurance or cardiovascular exercise, is any physical activity that uses the large muscles of the body in rhythmic, repeating motions and causes an oxygen deficit. The most effective types of aerobic exercise use the whole body and include walking, dancing, swimming, bicycling, mowing the lawn, and raking leaves. Many people with arthritis, although markedly deconditioned, can participate in aerobic exercise regularly and vigorously enough to improve health and function without exacerbation of their disease. Aerobic and strengthening exercise studies for persons with RA (Van Den Ende et al., 2000) and hip or knee OA (van Baar et al., 1999) present consistent evidence for the safety and benefits of exercise.

Decreasing pain and increasing activity, without correction of musculoskeletal biomechanics, may be detrimental to long-term outcomes, as demonstrated in a study of the effect of an NSAID on pain and walking speed (Schnitzer, Popovich, Andersson, & Andriacchi, 1993). The investigators studied biomechanical stresses at the knee joint before and after treatment and found that faster walking speeds associated with decreased knee pain resulted in increased joint stress in people with untreated knee joint malalignment.

Appropriately prescribed and implemented exercise is an important component of a successful arthritis treatment program. Table 23 presents details about the use of rest, physical activity, and exercise, with attention to the need for joint protection.

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Table 23. Joint Protection and Exercise Recommendations

Do	Avoid
<ul style="list-style-type: none"> • Select low-impact activities. • Condition muscles prior to vigorous activity. • Include flexibility and joint range of motion as key exercise components. • Reduce load on joint (e.g., body weight, exercise in gravity reduced environment such as pool or bike or rowing). • Select shoes and insoles for maximum shock attenuation during weight-bearing activities. • Evaluate for rigid/semi-rigid orthotics for biomechanical correction at ankles and knees. 	<ul style="list-style-type: none"> • Overstretching and hypermobility • Stairs, running, one-legged stance, and load carrying over 10% of body weight with hip or knee joint involvement • Deep knee bends • Squeezing rubber balls

Table 24 shows community resources often available for exercise programs. Types of exercise programs that can be used according to individual preference include water exercise, low-impact aerobic dance, tai chi, weight training, cardiovascular equipment such as bicycles and treadmills, and folk or square dancing.

Table 24. Community Resources for Exercise

- Arthritis Foundation exercise classes
 - Arthritis Foundation Aquatic Program
 - PACE (People with Arthritis Can Exercise)
- YMCA/YWCA
- Jewish community centers
- Community parks and recreation departments
- Hospital-based fitness/wellness programs
- Church, civic organizations

People with OA, RA, or JCA who have difficulty in maintaining minimum levels of physical activity should be referred to appropriate conditioning exercise opportunities in the community and their progress followed routinely by the healthcare team. When necessary to prepare an individual for successful participation in a community-based or self-directed exercise program, referral should be made for physical therapy and/or occupational therapy to evaluate and reduce impairments in range of motion, flexibility, strength, and endurance and instruct in joint-protection strategies.

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Physical Modalities

Physical interventions in conditions such as arthritis are aimed at decreasing impairment and improving function. These interventions may relieve pain independently or in combination with exercises. Because of the chronic and fluctuating nature of arthritis and the demonstrated effectiveness of self-management, pain relief measures that the person can learn to use independently should be encouraged. Recommendations from the healthcare provider should be accompanied by adequate demonstration, instruction, and follow-up.

Selection and successful use of a specific physical modality requires an appreciation that the physiologic components of pain may be musculoskeletal (e.g., muscle spasm, restricted movement, joint derangement, biomechanical stress, activity-related injury) as well as more direct consequences of the disease itself (e.g., metabolites, immune exudates, effusion). (See Table 9.) Expectations for pain relief should be realistic; relief of arthritis-related pain by passive means, such as application of heat or cold or electrotherapy, is short lived.

Heat. Heat can provide analgesia, promote relaxation, reduce muscle spasm, and enhance flexibility of muscle and periarticular structures (Michlovitz & Wolf, 1990). Heat commonly is used in combination with other interventions, most commonly stretching exercises. Superficial heat is delivered by radiation (light) or conduction (hot pack, paraffin, water). Superficial, local heat is the most commonly used thermal agent in both clinical and self-care settings (Davis, Cortex, & Rubin, 1990). Pain reduction was documented in clinical trials of two common forms of superficial heat: hydrotherapy (Hall, Skevington, Maddison, & Chapman, 1996) and paraffin (Dellhag, Wollersø, & Bjelle, 1992). Heat alone, however, produces only short-term, immediate pain relief. When heat is combined with an active exercise program (range of motion and strengthening) pain relief is greater, longer lasting, and improvements also occur in stiffness, strength, and function.

Deep heat in the form of diathermy (shortwave, microwave) and ultrasound requires professional application. In controlled trials, ultrasound was no better than placebo in an exercise program for knee OA (Falconer, Hayes, & Chang, 1992), and some studies reported increased pain with deep heat (Hashish, Harvey, & Harris, 1986; Ciccone, Leggin, & Callamaro, 1991). In a study comparing relative efficacy of ultrasound, shortwave diathermy and galvanic current in hip and knee OA, a majority of patients and physicians judged the benefits to be similar; however, shortwave diathermy was associated with worsening of symptoms (Svarcova, Trnavsky, & Zvatova, 1987). There is little scientific evidence that deep heat contributes to pain relief or improves exercise outcomes in arthritis.

Cold. Cooling has a local analgesic effect and reduces inflammatory responses secondary to trauma. The analgesic effect may arise from altered neural transmission, reduced muscle spasm, altered blood flow to muscle and nerve, or

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increased endorphin production (Michlovitz & Wolf, 1990). Cold is applied by cold packs, ice massage, immersion, or vapocoolant sprays. There is no evidence that a particular type of cold application consistently produces superior results. In the treatment of arthritis, pain relief, reduction of muscle spasm, and management of overuse injuries are the principal uses for cold therapy. Cold appears to be effective and well tolerated in both RA and OA (Clarke, Willis, Stenners, & Nichols, 1974; Kangilaski, 1981).

Superficial heat and cold have similar positive effects on pain, but there is no clear evidence that either alters immunologically-controlled inflammatory processes (Kangilaski, 1981). Pain reduction from these modalities is most likely due to effects on common sources of pain, muscle spasm, and activity-related trauma associated with biomechanical stress, shortened soft tissues, and fibrosis. Both modalities appear to be equally acceptable and effective in reducing pain and improving function when used in conjunction with an exercise program (Williams, Harvey, & Tannenbaum, 1986). An advantage of cold is its more immediate analgesic effect and reduction of post-traumatic inflammation and edema when applied shortly after an injury or surgical procedure. Heat has the advantage of producing an increase in connective tissue extensibility and promoting relaxation.

Electrotherapy. Transcutaneous electrical nerve stimulation (TENS) stimulates afferent nerve fibers that transmit or inhibit noxious input through the spinal cord to the brain (Hanegan, 1992). The initial rationale for TENS application arose from the gate control theory of pain. More recent work suggests that TENS also stimulates the sympathetic nervous system and brain stem nuclei to produce endorphins (Hanegan), and may inhibit arthritis-related inflammation (Levy, Dalith, Abramovici, Pinkhas, & Weinberger, 1987).

In RA, pain reduction, improved wrist function, and minimal adverse effects were reported for TENS (Abelson, Langley, Sheppard, Vlieg, & Wigley, 1983; Kumar & Redford, 1982). Effectiveness in OA is less clear. Results of controlled trials are inconsistent, with reports of both significant pain relief (Gemignani, Olivieri, Ruju, & Pasero, 1991) and no benefit above placebo (Lewis, Lewis, & Sturrock, 1984). There is no evidence to support claims that TENS technology used in the late 1970s and early 1980s or remote stimulation produce results superior to conventional TENS (Langley, Sheppard, Johnson, & Wigley, 1984; Mannheimer & Carlsson, 1979). Most reports of efficacy have come from studies using conventional frequency and waveform TENS at a submotor amplitude to produce a paresthesia or tingling sensation within the painful area (Foley, 1993). High frequency or burst mode TENS appear to provide relief lasting 2.5–18 hours and are the most appropriate modes for pain reduction in arthritis (Hayes, 1996).

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Iontophoresis uses direct current and phonophoresis uses ultrasound to introduce topically applied antiinflammatory agents through the skin. Although these procedures are used clinically for treatment of soft tissue inflammation and pain, most reports of effectiveness have come from case studies and uncontrolled trials. The few controlled trials have not demonstrated significant benefit (Ciccone et al., 1991; Vecchini & Grossi, 1984).

Low-energy laser has been studied in both RA and OA, with inconsistent results (Hall, Clarke, Elvins, & Ring, 1994; Heussler et al., 1993; Johannsen, Hauschild, Remvig, Johnsen, Petersen, & Bieler, 1994; Stelian et al., 1992). A meta-analysis of the evidence of laser efficacy in musculoskeletal pain management concluded that the use of laser treatment in these conditions cannot be recommended (Beckerman, die Bie, Bouter, De Cuyper, & Oostendorp, 1992).

Acupuncture. Acupuncture is a widely used therapy involving the insertion of slender needles at specified points on the body. The needles may be heated with an herb (a process called moxibustion) or electrified. Multiple studies have tested the effect of acupuncture treatment on OA pain and function, primarily of the weight-bearing joints, with mixed results. No clear benefit of acupuncture over sham acupuncture has been demonstrated to date (Ernst & White, 1998).

Orthotics

Orthotic devices include splints, braces, and other externally applied but removable devices that provide rest to inflamed painful joints, provide stability for unstable joints, and relieve pain. There are numerous types of orthotics, including the following:

- Compression gloves
- Elastic wrist extensions
- Resting hand splints
- Thumb post splints
- Functional/dynamic splints
- Orthotic devices in footwear
- Ankle foot orthoses
- Knee orthoses
- Spinal orthoses (cervical collar)

Some are prefabricated, but many need to be customized for the individual. Orthotics should be prescribed with consideration to appropriate fit, comfort, and cosmetic appearance.

Compression gloves and wrist orthoses. Compression gloves decrease pain and improve function by decreasing swelling in the fingers. In two controlled studies with RA patients, compression gloves significantly improved morning stiffness, pain, and nighttime throbbing compared with controls who wore non-compression gloves (Culic, Battaglia, Wichman, & Schmid, 1979; Oosterveld &

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Rasker, 1990). There were no measurable differences in hand volume, grip strength, pinch strength, or dexterity, and most patients did not elect to continue wearing the gloves after the study period. When hand or finger swelling is present, nighttime or 24-hour glove compression may provide symptomatic relief in some patients (Nicholas, 1994).

The use of elastic wrist extensor orthoses to decrease pain and increase function in people with RA was investigated in a small number of quasi-experimental studies that demonstrated improvements in pain and hand function (Kjeken, Moller, & Kvien, 1995; Nordenskiöld, 1990). Proper fit and patient preference are important factors in determining satisfaction with use (Stern et al., 1997).

Shoes. Shoes support and protect feet during ambulation on different walking surfaces, and their modification can be internal or external. Examples of internal modification are arch supports, metatarsal pads, a plastizote liner, and soft upper material. External modifications that may decrease foot pain include rocker soles, external metatarsal bar, and heel wedges.

Extra depth shoes and heat moldable shoes decrease pain and improve walking in persons with arthritis of the feet. A steel shank can be built into the sole of the shoe, stiffening the sole, thereby diminishing flexion at the metatarsophalangeal joints during the push-off phase of gait. Each of the orthotics or a combination of them can be used to relieve pain.

The use of wedged insoles to realign weight-bearing loads is effective in reducing pain in some people with OA of the knee. The best results were achieved by people with mild to moderate OA of the knee and a normal weight (Keating, Faris, Ritter, & Kane, 1993; Ogata, Yasunaga, & Nomiyama, 1997).

Assistive and adaptive aids. Canes, crutches, and walkers, when appropriately used, decrease pain and improve function, stability, and safety of ambulation. Canes increase the base of support and decrease pain by diminishing the ground reaction or weight-bearing load force on diseased joints of the legs. Canes also improve balance with additional proprioceptive input, compensate for weak muscles, and improve the stability of gait. The total length of the cane should be equal to the distance between the greater trochanter of the person's hip and the bottom of the shoe heel. When standing with the cane, the elbow should be flexed at 20 to 30 degrees and both shoulders should be level.

Proper instruction in cane use is important. The individual should hold the cane in the hand opposite the affected leg. The cane and the affected leg should be advanced together in a three-point gait pattern. When ascending stairs, the unaffected leg is advanced first. When descending, however, the cane and the affected leg lead. Saying "up with the good leg and down with the bad" is helpful for people to remember.

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The indications are similar for the use of crutches and canes. Axillary crutches are the most frequently used type of crutches—either one or two. It is important that most of the weight unloaded from the leg is borne by the hands, avoiding pressure on the axilla, which may compromise nerve function. Walkers provide the greatest stability, although the speed of ambulation is slow. They are helpful for bilateral leg involvement and provide safe independent ambulation. Adding a shelf to crutches and walkers allows individuals with severe wrist pain and weakness to walk.

A wheelchair or scooter greatly expands mobility in those with severe involvement and decreased endurance. Use of these ambulatory aids should be individualized.

Adaptive aids and assistive devices are equipment used to decrease pain and fatigue and increase independence in ADLs, such as personal hygiene, grooming, dressing, cooking, and homemaking activities. They reduce pain by decreasing mechanical stress on involved joints and by decreasing fatigue. (See Table 25.) Environmental modifications such as lower curbs, smaller steps, graded inclines, ramps, grab bars in bathrooms, raised toilet seats, guard rails, and nonslippery surfaces all are helpful in reducing pain-provoking postures and enhancing independent function.

Joint protection and energy conservation techniques are important for people with arthritis to incorporate in all daily activities.

Modalities with Insufficient Evidence for Recommendation

Collagen II, copper bracelets, and gold rings for the symptomatic treatment of RA have not demonstrated a consistent benefit or have not been studied adequately to recommend their use.

Magnet Therapy

There are two types of magnet therapy that have been used in OA and RA pain. One is a small, static magnet such as those worn as a bracelet, in the shoe, or taped to the knee. The second is pulsed bioelectric magnetic therapy, in which an electric current is directed at body tissues.

There have been a few well-designed studies of the use of pulsed magnetic field therapy that showed inconsistent results and strong placebo effects. Studies investigating the use of fixed or static magnets are even weaker (Leclaire & Bourgouin, 1991; Trock, Bollett, & Markoll, 1994; Trock, Bollet, Dyer, Fielding, Miner, & Markoll, 1993). There is insufficient evidence of the benefits of electromagnetic field therapy to recommend its use in the management of pain related to arthritis.

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Table 25. Examples of Assistive and Adaptive Devices

- Built-up longer handles on toothbrush, hairbrush
- Sponges and brushes
- Button hook, zipper hook
- Velcro fasteners on clothing, elastic shoelaces, sock aids
- Long handles on shoehorns, brushes, sponges
- Larger easily grasped handles on cooking utensils, knives, forks
- Padded pencils
- Jar openers
- Ergonomic work areas

Surgical Interventions

Recommendations in This Section*

21. For optimal functional results, people with disabling arthritis should be referred for surgical care prior to the onset of joint contracture, severe deformity, and advanced muscular wasting and deconditioning rather than as a last resort. (B)
22. Unless there are medical contraindications, most people with arthritis, including obese and older persons, should be referred for surgical treatment when noninvasive treatment is ineffective and function is impaired. (B)
23. Surgical intervention should be considered when pain and functional limitations prevent the minimum amount of activity recommended by the U.S. Surgeon General (30 minutes of exercise on most days of the week to maintain cardiovascular health). (B)

*Please note: Recommendations appear in bold type as they are discussed in the text. See Chapter II for an explanation of the strength of the evidence supporting the recommendations.

Indications and Timing

The ideal time to consider surgical intervention is often delayed and consequently many people who could benefit from surgery are discouraged from seeking it. This delay can lead to advanced muscle weakness and functional loss with further deconditioning as well as joint contracture, all of which can compromise the outcome of surgery (Fortin et al., 1999).

Procedures such as synovectomy, arthroscopic debridement, and total shoulder arthroplasty often have improved success rates earlier in the disease process prior to the development of tendon rupture, contracture, or advanced disease. Individuals who have total knee and total hip arthroplasty procedures prior to severe functional loss also have better outcomes than those treated at later stages (Fortin et al., 1999). In other people, surgery can be delayed without compromise

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and people given appropriate instructions about weight loss or physical conditioning to improve results when a procedure is performed at a later time. For these reasons, primary care clinicians should consider surgical referral earlier in the disease process and not only as a last resort.

Insurers may contribute to the delay because of their concern for the cost of surgery. Consideration should be given to the cost of long-term medication and assistive care, as well as decreased work productivity. Over time, such costs may exceed the cost of surgery. Total joint arthroplasty, specifically, has been shown to be a cost-effective treatment when compared to nonsurgical treatments (Hirsch, 1998; Rorabeck et al., 1994).

A decision for surgical treatment should be made on an individual basis with consideration of the following factors:

- Pain
- Function
- Deformity
- Stiffness
- Medical risk factors
- Patient goals and preferences
- Prior nonsurgical treatment
- Radiographic changes
- Age

Many of these factors can be assessed in the office. Medical risk factors, patient goals, prior nonsurgical treatment modalities, and pain are assessed during the history evaluation. Stiffness and some deformities are easily measured with a goniometer. Radiographic assessment of the leg should be done while the individual is weight bearing. Radiographic changes do not always correlate with pain level or extent of functional impairment (Dekker, Boot, van der Woude, & Bijlsma, 1992). Table 26 is an example of a brief assessment instrument for pain and function in the lower extremity.

Functional and muscular assessments are difficult to perform in an office and are therefore often overlooked, which is unfortunate because the muscle unit is the prime "engine" that will ensure the success of surgery on an arthritic joint. The person's current activity level and identification of activities discontinued due to pain should be clearly documented, particularly because there frequently is discrepancy between patient and physician assessment of morbidity (Kwoh et al., 1992).

Clinician-administered measures of pain and function can be used preoperatively as well as postoperatively. Some of these measures are designed for specific disease states such as arthritis or for specific anatomic areas, and others are more general. Many measures provide composite numerical scores, often with a

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weighting of approximately 40% for pain, 40% for function, and 20% for miscellaneous factors, although weights vary by assessment instrument. Scoring usually is done using a 100-point scale, and preoperatively patients often score in the 30s and 40s. Postoperatively such outcomes usually show marked improvement, particularly for total joint arthroplasty (Rorabeck et al., 1994). See Appendix B, Table 33, for a list of pain and function measurements and their properties.

Table 26. Assessment of Pain and Function of the Lower Extremity

1. Are you able to walk 1 mile?
2. Are you able to walk 6 blocks?
3. Do you have pain with every step taken?
4. Do you have pain at rest?
5. How long have you had pain?
6. Are you using pain medication and/or NSAID medication?
7. Do medications adequately relieve your pain?
8. Do you use a cane, crutch, or walker?
9. Do you have difficulty getting in and out of a car?
10. Do you have difficulty reaching your feet or putting on shoes?
11. Do you have difficulty bending, stooping, or climbing stairs?
12. What activities have you stopped due to your arthritis pain?

Patient self-administered measures are of value in functional assessment. Assessments should be done preoperatively to provide a basis for comparison with postoperative measurements. General measures, such as the SF-36 and Sickness Impact Profile (SIP), and measures more specific to arthritis, such as the WOMAC OA Index, Musculoskeletal Functional Assessment (MFA), and Arthritis Impact Measurement Scale (AIMS), can be used to document the effects of surgical treatment in arthritis patients. The MODEMS, developed by the American Academy of Orthopaedic Surgeons, also has demonstrated reliability and appropriate specificity for people with arthritis. An instrument developed for total joint arthroplasty can be used to assess patient recuperative power such as vigor in the immediate postoperative period (Keating et al., 1993).

Preoperative assessment in people with RA should include evaluation of the cervical spine because instability at the C1–C2 articulation may place the person at risk during induction of anesthesia. Radiographic assessment with flexion-extension cervical spine views or other assessment as deemed appropriate should be done preoperatively.

Exercise and Surgery

People with arthritis usually are deconditioned, and the decreased muscle strength is associated with higher levels of pain. With more advanced joint disease, a surgical procedure that eliminates pain can greatly facilitate the process of

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exercise and reconditioning. Some people whose disability has progressed to the point of nonambulation can be restored to ambulation by surgery. Studies of total hip arthroplasty have shown significant improvement in mean walking speed and other gait parameters (Rorabeck et al., 1994) and improvement in cardiovascular fitness (Ries, Philbin, Groff, Sheesley, Richman, & Lynch, 1997), even with older people (Brander, Malhotra, Jer, Heinemann, Stulberg, 1997). Following total knee replacement, there are significant improvements in quadriceps and hamstring muscle strength in 3 months (Sharma et al., 1996). Improved aerobic capacity has been documented in patients undergoing knee arthroplasty (Ries et al., 1996). The improved conditioning following exercise and surgical procedures has important implications for patients' longevity and comorbid medical conditions.

Unless there are medical contraindications, most people with arthritis, including obese and older persons, should be referred for surgical treatment when noninvasive treatment is ineffective and function is impaired. Surgical intervention should be considered when pain and functional limitations prevent the minimum amount of activity recommended by the U.S. Surgeon General (30 minutes of exercise on most days of the week to maintain cardiovascular health).

Total joint arthroplasty. Tables 27 and 28 summarize surgical procedures used for pain relief and functional improvements. Arthroplasty is the surgical restoration of the integrity and functional power of a joint or the creation of an artificial joint. Total joint arthroplasty of the hip and knee provide major improvement in musculoskeletal function. In most cases, pain relief is complete in the afflicted joint and quality of life is improved (Diduch, Insall, Scott, Scuderi, & Font-Rodriguez, 1997; Norman-Taylor, Palmer, & Villar, 1996; Ritter, Albohm, Keating, Faris, & Meding, 1995; Sharma et al., 1996).

The primary concern about total joint arthroplasty is polyethylene wear, in which small particles of polyethylene debris can incite an inflammatory response with the release of biologic factors. This can result in osteolysis of surrounding bone, which can lead to the failure of the total joint arthroplasty. People with RA who have arthroplasty show a less than 1% per year rate of failure (Wolfe & Zwillich, 1998). Young, highly active patients with OA have had higher failure rates in the past, but these rates are improving with newer surgical designs and improved materials (Diduch et al., 1997; Duffy, Trousdale, & Stuart, 1998). Studies with patients having total knee arthroplasty indicate a less than 1% per year failure rate (Duffy et al.; Wolfe & Zwillich) and low complication rates (Heck, Robinson, Partridge, Lubitz, & Freund, 1998). In one report of people under age 55, 99% of total knee prostheses survived after 10 years (Duffy et al.). Because of their documented effectiveness, total hip and total knee arthroplasty should be offered to patients when nonsurgical treatment

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Table 27. Surgical Procedures of the Lower Extremities, Pain Relief, and Functional Improvement

Procedure	Pain Relief	Function	Comment/Issues
Hip			
Total hip arthroplasty	Excellent	Excellent	Gold standard; revision possible; Polyethylene wear issues threaten longevity
Resection arthroplasty	Varies	Poor	Salvage procedure; severe limp
Arthroscopy	Varies	Varies	Not commonly used; some limitations in what can be accomplished
Arthrodesis	Good to excellent	Fair	Without hip motion; increased stress to back and knee
Osteotomy	Good in selected cases	Fair to good	Less predictable than total hip; indicated in select young active patients
Knee			
Total knee arthroplasty	Excellent	Excellent	Gold standard; revision possible; muscle rehabilitation by patient important; dependent on patient cooperation for rehabilitation
Resection arthroplasty	Fair	Fair	Salvage procedure; instability
Arthroscopy	Varies—often good	Varies	Commonly performed; minimum morbidity; may allow delay of total joint arthroplasty
Arthrodesis	Excellent	Poor	Durable function for weight-bearing ambulation; unacceptable to many patients; inability to sit in vehicles/theaters; more stress to hip; salvage after failed surgery
Osteotomy	Varies—often good to excellent	Good to excellent	Indicated in select young active patients; pain relief less predictable than total joint arthroplasty
Ankle			
Total ankle arthroplasty	Good to excellent	Good	Very high failure rate in past; renewed interest—still experimental; higher complication rate than other total joint arthroplasties
Arthroscopy	Varies	Varies	Diagnostic aid; limited morbidity; limited benefit in advanced disease

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Table 27. (cont.) Surgical Procedures of the Lower Extremities, Pain Relief, and Functional Improvement

Procedure	Pain Relief	Function	Comment/Issues
Arthrodesis	Good to excellent	Good	Stress transfer to midfoot and hindfoot; durable—withstands forces of gait; standard, accepted procedure
Osteotomy	Varies	Good	Not as commonly done as at the hip or knee
Hindfoot (Subtalar Joint)			
Arthroscopy (subtalar)	Varies	Varies	Limited ability to visualize joint; limited application; rarely used
Midfoot			
Arthrodesis	Good to excellent	Good to excellent	Standard of care; increases stress to adjacent joint; withstands weight-bearing forces; durable; beneficial; many different indications; reliable pain relief
Forefoot/metatarsophalangeal joint (MTPJ)			
Arthrodesis	Excellent	Good to excellent	Loss of motion MTPJ and limited heel height in shoe wear; durable; used for 1st MTPJ
Forefoot and Toes			
Resection arthroplasty	Excellent	Good to excellent	Very effective in relieving pressure areas in people with rheumatoid arthritis

becomes less effective and preferably before deconditioning becomes severe and difficult to reverse.

When considering total hip arthroplasty, there should be radiographic evidence of joint damage (NIH, 1994). Previous infection of the involved joint and patients' comorbidities may be contraindications for such procedures. Obesity and advanced age are not contraindications, because patients with these characteristics have success rates equivalent to other patients.

Total shoulder arthroplasty is effective in relieving pain (Connor & Bigliani, 1997). Functional results vary according to the status of the rotator cuff, which transmits shoulder muscle function to the proximal humerus. Individuals who have surgery before muscular function is lost can obtain restoration of function, including the ability to play golf (Connor & D'Alessandro, 1997; Jensen & Rockwood, 1998). People who are seen too late for restoration of muscular function still may obtain pain relief with shoulder arthroplasty.

Although total elbow arthroplasty is infrequently performed, the procedure can

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Table 28. Surgical Procedures of the Upper Extremities, Pain Relief, and Functional Improvement

Procedure	Pain Relief	Function	Comment/Issues
Shoulder			
Total shoulder arthroplasty	Good to excellent	Fair to excellent	Functional results depend on status of rotator cuff tendon and musculature
Resection arthroplasty	Unpredictable	Poor	Marked weakness; difficulty positioning hand in space; used only in salvage procedure
Arthroscopy	Varies—usually quite good	Varies—usually excellent	Frequently used for mechanical problems, joint decompression, spur removal; results often good; valuable in evaluation
Arthrodesis	Good	Fair to poor	Scapulohumeral motion is maintained, rarely performed; can be effective
Elbow			
Total joint arthroplasty	Good to excellent	Excellent	High failure rates in past, but current results greatly improved; excellent in rheumatoid arthritis and severe trauma
Resection arthroplasty	Unpredictable	Poor	Good for salvage procedure; rarely used
Arthroscopy	Varies—usually quite good	Varies—usually excellent	Can be used for removal of loose bodies, internal derangements, debridement
Arthrodesis	Excellent	Good	Compromises the ability to flex wrist
Wrist			
Total joint arthroplasty	Good	Good	Not commonly performed; tendon imbalance and loosening can detract from result
Resection arthroplasty	Good	Fair	Most commonly part, not all, of the eight wrist bones are removed (e.g., proximal row carpectomy); good salvage process
Arthroscopy	Good	Good	Useful for fibrocartilage tears/repair; excellent diagnostic tool
Arthrodesis	Excellent	Good	Most commonly only part of the wrist requires fusion leaving some motion possible; gold standard for rheumatoid arthritis
Hand Phalanges Metatarsophalangeal & Proximal Interphalangeal Joints			
Total joint arthroplasty	Good	Varies	May improve deformity; best at metatarsophalangeal joints; does not significantly improve function

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Table 28. (cont.) Surgical Procedures of the Upper Extremities, Pain Relief, and Functional Improvement

Procedure	Pain Relief	Function	Comment/Issues
Resection arthroplasty	Fair	Fair	Tendon may be used as interposition; some weakness in function; has been supplanted by implant arthroplasty
Arthroscopy	N/A	N/A	In developmental stage—not commonly performed
Arthrodesis	Excellent	Limits motion	Durable strength maintained; metatarsophalangeal of thumb commonly performed; good salvage procedure, especially distal interphalangeal joints

provide effective pain relief and improved function (Connor & D'Alessandro, 1997; Leber & Melone, 1988; Lee, 1999). Total ankle arthroplasty was abandoned 20 years ago by most surgeons because of high failure rates. It is being tried again, but at this time the procedure is experimental (Kofoed & Sorensen, 1998).

Resection arthroplasty. Resection arthroplasty is the removal of the diseased joint surface without replacement with artificial material. The procedure is not commonly done. It may be used in the leg after the removal of a failed total joint arthroplasty due to infection or insufficient bone for successful prosthesis support. Although pain relief and functional benefit are considerably inferior to that of a successful total joint arthroplasty, sufficient benefit may occur to allow ambulation. In the arm, strips of fascia or tendon may provide a biologic material that acts as a spacer to allow some joint motion without bony impingement.

Arthroscopy. Arthroscopy is the examination of the interior of a joint using an endoscope that is inserted into the joint through a small incision. With the aid of the arthroscope, surgical procedures can be performed percutaneously. Joint arthroscopy was developed initially for the knee, but now is commonly performed in the shoulder, elbow, wrist, and ankle and less commonly in the hip, subtalar joint, and smaller joints of the hand. It is often beneficial as a diagnostic aid, including biopsy, and in the treatment of mechanical derangements such as the removal of loose bodies and torn menisci. Arthroscopy has minimal post-operative morbidity in comparison with arthroplasty.

There is a role for arthroscopic debridement in patients who wish to postpone arthroplasty. Linschoten and Johnson (1997) found that 50%–70% of these patients have good results that last for several years. Longstanding symptoms, severe arthritic changes on radiograph, and malalignment are more frequently associated with poor results (Baumgaertner, Cannon, Vittori, Schmidt, &

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Maurer, 1990) and may be better treated with total joint arthroplasty. Arthroscopic debridement often is a temporizing procedure that provides significant benefit and reduced pain (Linschoten & Johnson).

In people with RA, arthroscopic synovectomy can provide temporary relief of symptoms for several years (Fiocco et al., 1996; Ryu, Saito, Honda, Shinakura, & Sano, 1995; Sharma et al., 1996). The arthroscopic technique has less post-operative pain and morbidity than an open synovectomy (Ryu et al.; Smiley & Wasilewski, 1990) but may be associated with a higher rate of symptom recurrence (Ryu et al.). Arthroscopic debridement has palliative value as a procedure (Ogilvie-Harris & Basinski, 1991).

Arthrodesis. Arthrodesis is the surgical removal of the articular surface and fixation of the two bones to promote bone fusion at the prior joint. The indication for arthrodesis is functional impairment and pain in a joint not sufficiently relieved by nonoperative treatment. Improved fixation techniques provide a rate of union above 90% in most treated joints. Following arthrodesis most patients are restored to brace-free function and many return to high-level activities such as physically demanding employment (Glick, Morgan, Myerson, Sampson, & Mann, 1996). Some are able to engage in competitive sports. Pain relief following arthrodesis of an arthritic joint usually is complete or nearly complete. This often results in functional benefit and allows a return to more normal function despite the loss of motion in the affected joint. Joints treated with total joint arthroplasty (i.e., hip, knee, shoulder, and, less frequently, the elbow) are treated rarely with arthrodesis. Joints where replacement is not an option are treated with arthrodesis. This includes the subtalar, calcaneocuboid, talonavicular, mid-foot joints of the feet, and the lesser joints of the hands and feet. The joints that cause the greatest functional deficit with arthrodesis (i.e., the hip and knee) are the ones in which total joint arthroplasty is most successful. Joints where arthroplasty is possible but less successful usually are treated with arthrodesis. These joints include the wrist, ankle, great toe metatarsophalangeal joint, and smaller joints of the hand (Felix & Kitaoka, 1998). At the wrist a limited fusion of only some of the eight bones may provide sufficient pain relief while still preserving partial range of motion.

People with OA, particularly those with inflammatory arthritis, may have persistent pain from more than one joint. In the ankle, hindfoot, and midfoot, where there are joints in close proximity it may be difficult to determine which joint is the source of the most pain. Standard foot and ankle radiographs often do not provide a clear assessment of arthritic changes that tend to be less apparent in these locations. The selection of a specific arthrodesis should be made with the aid of additional tests when standard office assessment and radiographs do not provide sufficient information.

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Special radiographic views can be obtained to delineate more precisely specific joints. Computed tomographic scans of the hindfoot and midfoot may be helpful. Bone scintigraphy frequently is beneficial in determining which joints are most involved. Anesthetic block of a specific joint with radiographic guidance for confirmation of the proper location can be diagnostic in determining the precise location of pain. Once the source of pain is determined with the aid of a bone scan and confirmed pain relief is found with a selective block of the specific joint by a radiologist, the likelihood for more permanent pain relief with an arthrodesis is greatly enhanced.

Osteotomy. Osteotomy is the surgical division or sectioning of bone. It is most commonly used in the leg. Osteotomy about the hip and knee can provide significant pain relief in selected individuals (D'Souza, Sadiq, New, & Northmore-Ball, 1998; Rinonapoli, Mancini, Corvaglia, & Musiello, 1998). This procedure may be considered for young, more active people for whom the longevity of total joint arthroplasty would be in question and revision more likely. Osteotomy is contraindicated in individuals with inflammatory arthritis. For people with OA in which the disease is localized to one area of the joint, an osteotomy can help unload that area of the joint, shifting more stress to a less diseased portion. At the hip, this may be done with varus or valgus femoral osteotomy or a pelvic osteotomy, provided there is concentricity in the new area of the femoral head, which will be placed in a more weight-bearing position in a contained acetabulum. At the knee, distal femoral or, more frequently, high tibial osteotomy may be performed. An osteotomy is used most frequently in the varus knee with uni-compartmental medial gonarthrosis. Longer healing times, slower resolution of pain, and lower percentages of patients with pain relief compared with total joint arthroplasty make these procedures less popular options for people with OA. In a young, active person, however, deferral of total joint arthroplasty is desirable and an osteotomy may give significant pain relief while postponing an arthroplasty.

Bone removal procedures. Exostectomy is the removal of bone. Areas of bone prominence may become extremely painful, particularly when aggravated by weight bearing during ambulation. Such deformities are common in people with OA and in people with RA who frequently develop hand and foot deformities, which cause both functional impairment and pain. Exostectomy, especially in the foot, may improve the ability to wear shoes comfortably and greatly reduce pain during ambulation.

A condylectomy is the removal of a prominent part of the bone (condyle) at the joint surface. The condyles may cause areas of increased pressure and resulting pain particularly in the plantar surface of the foot. Partial phalangectomy is a removal of part of the small bones (phalanges) of the hands and feet. When there are severe deformities of toes, such as claw toes, parital phalangectomy, which may be combined with tendon transfer, may allow correction of deformity with subsequent pain relief.

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Soft tissue procedures. People with RA are prone to tendon rupture. Tendon repair often is indicated when rupture or long-term functional loss occurs. Tendon releases, lengthenings, or transfers also may be used to correct deformity and improve function. Restoration of thumb function can be performed with tendon transfer in a person with RA.

Because of the associated tenosynovitis, people with OA are prone to carpal tunnel syndrome, a compressive neuropathy of the median nerve at the distal wrist and hand. When injections or splints do not provide relief of symptoms, carpal tunnel release in most cases will provide excellent relief of pain, paraesthesias, and numbness. If the condition is inadequately treated so that functional loss such as muscle atrophy occurs, surgical release may provide suboptimal results. **Therefore, appropriate surgical referral should be made prior to the onset of irreversible changes.**

Nerve releases also are performed in the leg. Although less predictable, tarsal tunnel release at the level of ankle and medial foot may provide relief of pain and paraesthesias particularly if there is a space occupying lesion or extensive tenosynovitis.

Finally, removal of rheumatoid nodules can provide relief of pain in patients where these cause impingement. This is more likely in the foot where the covering of the shoe may rub against such nodules.

Miscellaneous procedures. There are numerous additional surgical procedures that can provide benefit for a person with arthritis. People with RA frequently have hand and forefoot deformities, such as severe claw toes, with excessive pressure over the tip of the proximal interphalangeal joints and excess pressure under the plantar condyles. Small joint arthroplasty or arthrodesis can improve hand function and pain. In the foot, claw toe deformities in association with excessively prominent and painful metatarsal heads (metatarsalgia) are seen in patients with OA and are very common in patients with RA. Arthrodesis of the first metatarsophalangeal joint provides a stable platform and relieves arthritic pain during the push-off phase of gait. This helps restore weight-bearing function to the medial side of the foot. The addition of resection arthroplasty, that is, removal of the overly prominent lesser metatarsal heads, can provide complete or nearly complete pain relief for patients with severely disabling metatarsalgia (Mann & Thompson, 1997).

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V. Treatment of Pain in Children and Older Adults with Arthritis

Recommendations in This Section*

24. The assessment of pain should be ongoing in any child with juvenile chronic arthritis (JCA). A comprehensive and developmentally appropriate pain assessment should incorporate a pain history, the child's self-report, behavioral observations, parents' assessment, and physiologic cues. (Panel consensus)
25. Analgesia for children should be similar to that for adults who experience pain. (Panel consensus)
26. Patient/family education should be provided on an ongoing basis to increase self-care skills and feelings of self-efficacy and to develop self-advocacy skills for negotiating with the healthcare system. (Panel consensus)
27. Cognitive-behavioral therapy (CBT) should be used to reduce pain and psychological disability and to enhance self-efficacy and pain coping for children. (B)
28. Appropriate interventions to minimize pain and anxiety related to diagnostic and therapeutic procedures should be an integral part of the management of children with arthritis. The child and parent should be adequately prepared for any procedure, and interventions should be individualized for the child and the procedure and administered prophylactically. (B)
29. Whenever conscious or deep sedation is required to perform any procedure, the guidelines developed by the American Academy of Pediatrics for patient monitoring and resuscitative equipment should be followed. (B)
30. The antiinflammatory and analgesic benefits of nonsteroidal antiinflammatory drugs (NSAIDs) should be weighed against the potential risk, particularly in older people. In the person who is at increased risk for a serious upper gastrointestinal (GI) adverse event, gastroprotective agents should be used even if nonselective agents are given at low doses. (B)

*Please note: Recommendations appear in bold type as they are discussed in the text. See Chapter 11 for an explanation of the strength of the evidence supporting the recommendations.

JCA is the most common chronic rheumatic condition in childhood, affecting approximately 285,000 children in North America. It is the fifth most prevalent chronic disease of childhood (Cassidy & Petty, 1995). The major kinds of JCA include pauciarticular (four joints or less), polyarticular (five joints or more, which is also divided into those with and without rheumatoid factor), systemic (associated with high-spiking fevers and a plethora of other systemic manifestations commonly including a fleeting rash, pericarditis, hepatosplenomegaly, and

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anemia), psoriatic arthritis, spondyloarthropathy (frequently presenting as peripheral arthritis), reactive arthritis, and arthritis associated with inflammatory bowel disease. The most common forms of juvenile arthritis (pauciarticular and polyarticular) commonly develop in girls 1–3 years of age. Boys equal the number of girls with systemic disease and outnumber girls with spondyloarthropathies. In contrast to adults, 30%–50% of children go into remission after several years, depending on subtype. Reactive and pauciarticular arthritis are the most likely to go into remission. Rheumatoid factor positive polyarticular arthritis and prolonged systemic arthritis are the most chronic and destructive forms of the disease.

Most children with JCA experience pain, stiffness, and joint discomfort but differently from adults with arthritis (Hagglund, Schopp, Alberts, Cassidy, & Frank, 1995; Schanberg, Lefebvre, Keefe, Kredich, & Gil, 1997). The intensity of pain is not always correlated with the degree of arthritis (Howite, Walco, & Pochaczewsky, 1992; Schanberg et al.; Vandvik & Eckblad, 1990). Children usually report less pain, and many have substantially fewer joints with arthritis than do adults (Truckenbrodt, 1993). Some children have painless arthritis. In one study, 26% of children with pauciarticular arthritis, 3% with polyarticular arthritis, and 4% with systemic onset arthritis reported no pain (Sherry, Bohnsack, Salmonson, Wallace, & Mellins, 1990).

Assessing the meaning of pain to the child and family and how it affects their daily lives helps the clinician understand the pain from the child's and family's perspective and demonstrates the clinician's desire to ease pain and disability. This is easier in verbal children, so special attention to pain, anxiety, and despair should be given to children who are nonverbal or noncommunicative. Pain and discomfort can exist in the absence of immediately apparent signs (Table 29).

Assessment in Children

The assessment of pain should be ongoing in any child with JCA. Open communication about pain and discomfort among the child, family members, and clinicians is paramount. Basic information concerning the preferred terms for pain (e.g., "owwie" or "boo-boo"), to whom the child best communicates pain, and past pain experiences are central to assessment. Other information such as expectations (e.g., anticipating either having or not having a procedure done) and individual preferences for assessing and treating pain should be incorporated into both immediate and long-term pain management plans.

Methods of Pain Assessment

Children's cognitive and psychosocial development affects their expressions and understanding of pain and influences their strategies for coping with pain. Understanding how children's developmental characteristics influence pain will

Table 29. Misconceptions About Pain in Children

Misconception	Fact
Infants and children do not feel pain or do not feel pain as intensely as adults.	Research has shown that full-term and preterm newborns exhibit physiologic, biochemical, and behavioral responses to pain (Anand & Hickey, 1990; Barlier, Attia, Mayer, Amier-Tison, & Snider, 1989; Menon, Anand, & McIntosh, 1998; Porter, Grunau, & Anand, 1999). Sensitivity to pain decreases with age, with younger children exhibiting a lower pain threshold than older children (Lander & Fowler-Kerry, 1991).
Infants and young children do not remember pain.	By 6 months of age, infants consistently avoid painful stimuli they have experienced in the past, demonstrating their memory of painful stimuli (Johnston, 1993; Porter et al., 1999).
Children cannot communicate where they hurt or the intensity of their pain.	Children beyond infancy can accurately point to the location of their pain on their body or mark the site on a drawing (Savada, Tesler, Holzemer, Wilkie, & Ward, 1989). By age 4 years, most children can use simple self-report pain scales (Matthews, McGrath, & Pigeon, 1993).
If behavioral manifestations of pain are not present, then the child is not experiencing pain.	Studies have shown that children can experience pain without displaying the behaviors commonly associated with pain (Schechter, Bernstein, Beck, Hart, & Scherzer, 1991). Children use sleep and play as coping mechanisms to deal with pain.
Children will always tell the truth about pain.	While children rarely fabricate pain, they may underreport or deny pain for fear of injections or other painful procedures (Hildeout, 1997).
Opioids can lead to addiction and respiratory depression in children.	Opioids can be safely given to neonates, infants, and children. There are virtually no reports of addiction in children treated with opioids for pain management, and reports of respiratory depression are rare (Menon et al., 1998; Whaley & Wong, 1991).

assist clinicians to assess and manage their pain. Children's conceptualizations of pain correspond to Piaget's stages of cognitive development, shifting from concrete, perceptually dominated concepts in younger children to more generalized, abstract, and psychologically oriented concepts in older children (Gaffney, 1993).

A comprehensive and developmentally appropriate pain assessment should incorporate a pain history, the child's self-report, behavioral observations, parents' assessment, and physiologic cues. Valid and reliable assessment tools are available for measuring pain intensity and pain affect in children. These include child self-report, parent report, and behavioral observation tools. (See Appendix A, Table 31.) Because pain is a subjective phenomenon, self-report should be used as the primary source of pain assessment whenever possible. Behavioral observations and physiologic cues can provide additional information, but should not be used as the primary source of pain assessment. The exception is preverbal children and nonverbal or cognitively impaired individuals, for whom behavioral observations should be the primary source of

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assessment by the clinician, with parent or primary caregiver's assessments providing additional information. Physiologic signs such as heart rate and blood pressure are the least reliable measure of pain in children and should be used only as helpful adjuncts in assessing pain; they should not be used as the primary source of information.

Obtaining a thorough pain history is important in assessing pain. Information should be elicited about the child's understanding of pain, previous pain experiences and pain responses, and strategies for coping with pain, as well as a parental pain history. (See Appendix A, Table 32.) Both the child and parents should be included in pain assessment. Parents can provide important information about the child's previous experiences with pain and often are able to predict their child's responses to pain.

Self-Report and Proxy Report

In children over 4 years of age, self-report provides the most reliable and valid estimate of pain intensity and location. By this age most children have acquired the necessary cognitive and communication skills needed to use self-report pain assessment tools. Children rarely fabricate pain but may underreport it for fear of a painful procedure (e.g., joint injection) or because of a desire to please others. Children also may imitate their parents' responses to pain. Some children cannot express pain to the healthcare team but may confide in their parents who can relay the child's thoughts and feelings. Some especially shy or anxious children will not respond either verbally or by pointing to a scale. Appropriate methods for these young children include the Oucher (Beyer, Denyes, & Villarruel, 1992), Wong-Baker Faces Pain Rating Scale (Wong & Baker, 1988), and the Poker Chip Tool (Hester, Foster, & Kristensen, 1990). Figure 10 is an example of an assessment tool that can be used with young children. Cartoon faces as measurement scales for pain may measure pain affect or the intensity of pain, anxiety, or distress.

Children over the age of 7 years usually understand the concepts of order and number, and thus can use a numeric rating scale, a horizontal word graphic rating scale, or a visual analog scale—although this last scale was the least preferred in one large study of pediatric patients (Tesler, Savedra, Holzemer, Wilkie, Ward, & Paul, 1991). Location of the pain can be determined either by asking the child to point to the body part or by use of a body map colored with different colors to indicate different pain types or intensities.

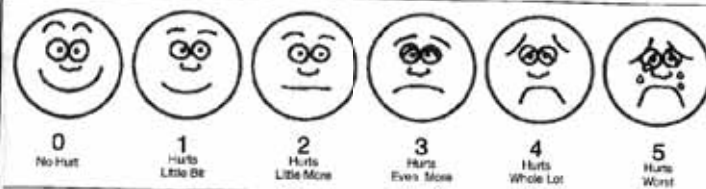
The Varni/Thompson Pediatric Pain Questionnaire (PPQ) is both a self-report and a parental report that has been used extensively in children with arthritis (Thompson & Varni, 1986). This instrument includes visual analog scales, a projective color body map, and a list of pain descriptors. Parental report regarding pain in children with arthritis correlates well to physician and patient reports

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Figure 10. Wong-Baker Faces Pain Rating Scale

Explain to the person that each face is for a person who feels happy because he has no pain (hurt) or sad because he has some or a lot of pain. Face 0 is very happy because he doesn't hurt at all. Face 1 hurts just a little bit. Face 2 hurts a little more. Face 3 hurts even more. Face 4 hurts a whole lot. Face 5 hurts as much as you can imagine, although you do not have to be crying to feel this bad. Ask the person to choose the face that best describes how he is feeling. Rating scale is recommended for persons age 3 years and older.

Brief word instructions: Point to each face using the words to describe the pain intensity. Ask the child to choose face that best describes own pain and record the appropriate number.

Note: From Wong, D.L., Hockenberry-Eaton, M., Winkelstein, M.L., Schwartz, P.: Wong's Essentials of Pediatric Nursing, 6th St. Louis, 2001, p. 1301. Copyright by Mosby, Inc. Reprinted by permission.

(Ilowitz et al., 1992), although one study reported good correlation between mother and child reports of disability but not pain (Doherty, Yanni, Conroy, & Bresnahan, 1993).

Behavioral Observation and Pain Coping

Limitations in children's cognitive and verbal development affect both their understanding of pain and their ability to communicate their discomfort. Therefore, behavioral observation is the primary assessment approach for non-verbal children and enhances the assessment of pain in verbal children. Pain behaviors shown to be reliable and valid pain measures in children with JCA include guarding, bracing, active rubbing, rigidity, and single and multiple flexing (Jaworski, Bradley, Heck, Roca, & Alarcon, 1995).

Pain is a major cause of disability in children with JCA, and the inability to engage in usual and desired activities affects pain perception. Thus, assessment of the child's functional status is an essential component of a comprehensive pain assessment. Several pediatric-specific instruments have been developed to measure functional status in children with rheumatic diseases. (See Appendix B, Table 34.)

The Pediatric Pain Coping Inventory to assess pain coping strategies was validated in children and adolescents with arthritis (Varni et al., 1996). It includes a parent report and can be used in children as young as 8 years. Children with higher pain coping skills and rational thinking report less pain (Schanberg et al., 1997).

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Pain Management in Children

Pain Management Associated with Juvenile Chronic Arthritis

Control of JCA is primary to the treatment of pain and to lessen future problems with destruction of the joint. There are children in whom treatment of their JCA is unsatisfactory and a few who do not tolerate available treatments. Adverse effects of treatment may lead to either acute pain (e.g., gastritis) or chronic pain (e.g., avascular necrosis, compression fractures). As with adults, pain should not be ignored while waiting for systemic antiarthritic treatment to take effect because some of these agents may take months for their full benefit to be realized. To manage pain adequately, a trusting relationship should exist among the child, family members, and healthcare team. No one solution fits all, and only through open discussion and negotiation will the best outcome for each child and family member be reached.

Analgesic Management of Pain

In general, analgesia for children should be similar to that for adults who experience pain. There are, however, few studies on pain management in childhood arthritis. The two mainstays of initial treatment for most children are NSAIDs and intra-articular corticosteroid injection (Cron, Sharma, & Sherry, 1999). NSAIDs are effective in reducing the number of tender joints and decreasing morning stiffness. There are no published studies of the cyclooxygenase-2 (COX-2) selective NSAIDs in children, and these medications are not approved by the Food and Drug Administration (FDA) for use in children.

Intra-articular injections are reported to lead to local disease remission, but the effect on pain has not been studied systematically. Triamcinolone hexacetonide is the agent used in most studies; it is superior to hydrocortisone and lasts longer than methylprednisolone acetate or triamcinolone acetonide. Leg length discrepancy was significantly reduced in one study of young children injected early in the course of JCA and repeated with each occurrence of arthritis (average of 3.25 injections over 42 months) compared to children treated with NSAIDs alone, which suggests a shorter duration of JCA in those injected (Sherry, Stein, Reed, Schanberg, & Kredich, 1999). Thus, intra-articular corticosteroid injection should be considered in children with limited painful arthritis.

If the child does not respond to the initial therapeutic steps, the child's condition should be reevaluated, because some of the pain may not be arthritis related. Mood and stress also influence children's pain perceptions, so interventions to manage mood disturbances and daily stress should be a part of the comprehensive approach to pain management.

If the arthritis continues to cause unremitting pain, analgesics such as tramadol or an acetaminophen and oxycodone combination should be administered, in

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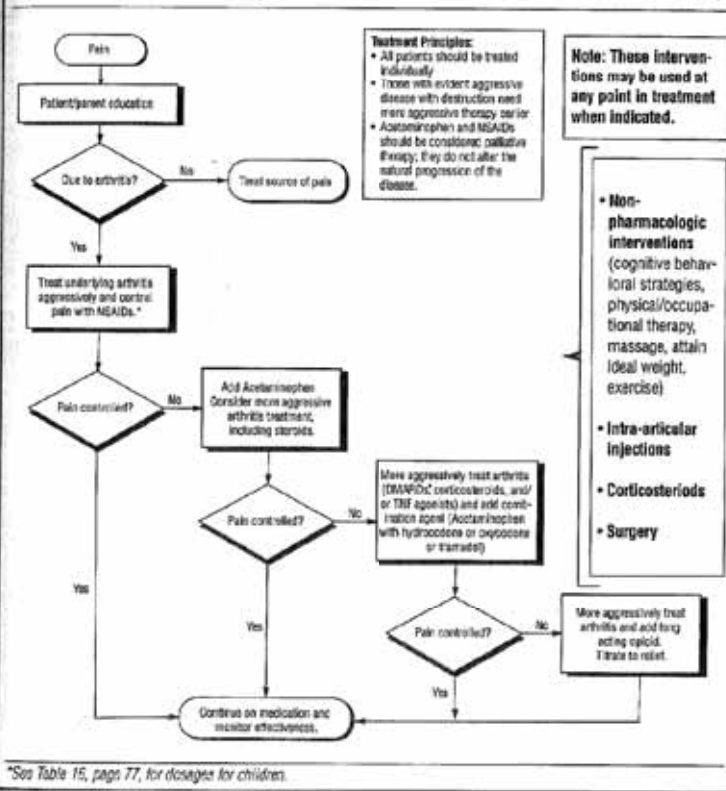
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addition to more aggressive treatment of the underlying disease with disease-modifying antirheumatic drugs (DMARDs), corticosteroids, and/or tumor necrosis factor agonists. If these therapies do not achieve adequate pain control, opioids should be used for the child who experiences moderate to severe pain related to arthritis. Oral administration is preferable, using a long-acting preparation on a scheduled basis. Figure 11 presents an algorithm for the management of pain in children with arthritis. Table 11 (page 59) presents dosing recommendations for use of analgesic medications in children.

DMARDs and glucocorticosteroids. Studies of the traditional DMARDs (e.g., sulfasalazine, methotrexate) in children with JCA do not report effects on

Figure 11. Algorithm for Management of Pain in Children with Juvenile Chronic Arthritis*



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pain but, similar to adults, many children experience substantial improvement when using these agents. One study of hydroxychloroquine did not show increased benefit over placebo in reducing the degree of arthritis but did show decreased pain (Brewer, Giannini, Kuzmina, & Alekseev, 1986). Etanercept, compared with placebo, significantly decreased both the degree of arthritis and pain (Lovell et al., 2000). Agents such as leflunomide and cyclosporine have not been studied in children.

Glucocorticosteroids may have a role in children who experience marked morning stiffness and pain as well as in children who are begun on slower-acting agents such as methotrexate (subcutaneously) or sulfasalazine, but the benefits should outweigh the risks of osteoporosis, growth retardation, and other steroid effects (Kvien, Hoyerdal, & Sandstad, 1982). Rarely will a child require chemotherapeutic medication such as azathioprine, mycophenolate mofetil, cyclophosphamide, or stem cell transplantation.

Physical and Occupational Therapy

Physical and occupational therapy, including modalities such as splinting, ice, heat, paraffin baths, massage, prone lying, active exercise, and stretching have been shown to be useful for pain management in adults, but no studies have rigorously evaluated the benefit of such therapy in children. Joint protective techniques may help reduce the pain of activities of daily living and decrease strain across inflamed or damaged joints. Aerobic conditioning may improve energy, increase the child's sense of well-being, and help decrease pain. A study of 25 children with polyarticular JCA found that a structured physical conditioning program improved aerobic endurance without increasing disease activity or pain (Klepper, 1999). Ultrasound and transcutaneous electrical nerve stimulation generally are not used for pain control in children with arthritis.

Surgery

Surgery is an appropriate treatment for children with either destroyed, painful joints or recurrent arthritis unresponsive to medical therapy. Marked pain reduction has been reported following synovectomy of the elbow, knee, and proximal interphalangeal joints in children (Lonner & Stuchin, 1997; Rydholm, Elborgh, Ranstam, Schroder, Svantesson, & Lidgren, 1986; Wilde, 1974; Wilson, Arden, & Ansell, 1973). Soft tissue release of the hips decreased pain immediately and long term (Mogensen, Brattstrom, Ekelund, Svantesson, & Lidgren, 1982; Swann & Ansell, 1986; Witt & McCullough, 1994). As in adults, total joint replacement in children usually is effective in relieving pain (Haber & Goodman, 1998; Witt, Swann, & Ansell, 1991). Whenever possible, joint replacement surgery should be delayed until closure of the growth plates has occurred.

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Patient/Family Education

Patient/family education should be provided on an ongoing basis to increase the child's and parents' self-care skills in pain management, feelings of self-efficacy, and ability to negotiate with the healthcare system. Patient/family education should focus on understanding and managing the child's arthritis and related pain, health promotion, growth and development issues, disease prevention, and self-care and self-advocacy skills. Clinicians should help parents to encourage their child to participate in managing their JCA and pain to promote eventual independence in self-care. The book *Raising a Child with Arthritis: A Parent's Guide*, available from the Arthritis Foundation, is a good resource for families.

When the child's pain or disease activity interferes with his or her school performance, the child should be referred for physical or other health impairment (POHI) services under the Individuals with Disabilities Education Act (IDEA) (1997), formerly known as The Education for All Handicapped Children Act of 1975 (P.L. 94-142). This law applies to children who attend federally funded schools and requires that schools provide special services to children ages 3–21 years with emotional, mental, or physical impairments whose condition interferes with their ability to function in school. These services may include (a) adaptive physical education, (b) occupational therapy, (c) physical therapy, (d) speech therapy, and (e) transportation to and from school. In addition, IDEA requires that individualized transition plans be developed for every POHI student by the age of 14–16 years.

Cognitive-Behavioral Therapy

CBT should be used to reduce pain and psychological disability and to enhance self-efficacy and pain coping. Children's strategies for coping with pain are influenced by age, level of cognitive development, emotional state, temperament, culture, and health status, as well as previous experiences with pain, parental attitudes, and environmental and situational factors. Studies of children with cancer, headache, and other painful conditions report reduction in pain using strategies such as distraction, humor, relaxation exercises, allowing the parent to be present during painful procedures to provide psychological support, and allowing the child some degree of control over what is happening.

Some studies have focused on cognitive-behavioral aspects of pain and pain management in children with rheumatic diseases. A study of 13 children with juvenile rheumatoid arthritis (RA) showed significant pain reduction both short term and at 12 months with eight sessions of CBT that used progressive relaxation, meditative breathing, and guided imagery (Walco, Varni, & Howite, 1992). Progressive muscle relaxation and guided imagery techniques reduced pain and improved function in seven girls with juvenile fibromyalgia (Walco et al.). Strategies such as distraction, visual imagery, hypnotic suggestion, and

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behavioral management may be more effective with younger children, whereas older children may benefit more from strategies such as progressive relaxation and meditative breathing.

Procedural Pain in Children

Procedural pain is a major issue for children. Children, especially younger ones, do not give assent and do not understand the reasons for painful procedures, nor that these procedures are short lived.

Young children have been found to exhibit more distress during invasive procedures and rate procedure-related pain higher than older children (Kazak, Penati, Brophy, & Himelstein, 1998; Wong & Baker, 1988). Interventions to minimize pain and anxiety related to diagnostic and therapeutic procedures should be an integral part of the management of children with arthritis. Interventions for managing procedural pain should be individualized for the child and the procedure and administered prophylactically.

Numerous nonpharmacologic interventions have been shown to be effective in helping children cope with procedural pain and anxiety. Such strategies include providing age-appropriate information about the procedure, distraction, relaxation exercises, guided imagery, and hypnosis. The child and parent should be provided with accurate information about what will be done and what the child may experience during the procedure (McCarthy, Cool, & Hanrahan, 1998). Allowing the child to role play the procedure before it is performed familiarizes the child with the medical equipment that will be used and allows them to rehearse effective coping strategies to use during the procedure (McCarthy et al.). Whenever possible, parents should be allowed to remain with their child during the procedure to provide comfort and support, which, in turn, will minimize the child's anxiety.

Children with arthritis frequently have repeated blood tests, and many receive subcutaneously administered medication (methotrexate and etanercept). Topical anesthetic agents, ice, and cognitive-behavioral techniques may be beneficial for minimizing pain during these procedures. Lidocaine/prilocaine cream is safe and effective in preventing pain associated with minor procedures such as venipuncture, lumbar puncture, and subcutaneous drug reservoir injection (Arts et al., 1994; Taddio, Nulman, Goldbach, Ipp, & Koren, 1994). Iontophoresis produced rapid, safe, and effective topical anesthesia in children prior to minor invasive procedures (Squire, Kirchhoff, & Hissong, 2000; Zempsky, Anand, Sullivan, Fraser, & Cucina, 1998). One study showed that adding 0.1 ml of 1% lidocaine to injectable gold decreases pain (Kovalesky, Sherry, & Lehman, 1986).

Children with JCA may require multiple joint injections over the years, so every effort should be made to make this procedure as comfortable as possible. Cognitive-behavioral interventions and topical anesthetics may be effective in minimizing the

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pain associated with arthrocentesis. Local anesthesia with topical anesthetic preparations followed by buffered lidocaine can help children to have minimal discomfort. In young children undergoing one or a few joint injections, conscious sedation with oral midazolam 0.2–0.3 mg/kg, may relieve anxiety. Children requiring many joint injections or who are distraught with the idea of injections may require brief general anesthesia. It usually takes an experienced rheumatologist only a few minutes to inject the joints once the child is anesthetized. **Whenever conscious or deep sedation is given, the guidelines developed by the American Academy of Pediatrics for patient monitoring and resuscitative equipment should be followed** (American Academy of Pediatrics Committee on Drugs, 1992).

Pain Assessment and Management in Older Adults

Because osteoarthritis is a disease most often seen in older adults, much of this guideline is applicable to the assessment and management of arthritis-related pain in that population. There are, however, several aspects of pain management that should be particularly emphasized in older adults.

It has been well established that chronic pain is common in older people (American Geriatric Society, [AGS] 1998) and that arthritis is one of the most common sources of pain. Pain is common both in community-dwellers and in people in nursing homes, where 80%–85% of the residents are reported to have substantial pain that is undertreated (Ferrell, Ferrell, & Osterweil, 1990). The ability to assess and manage pain in older adults is complicated by the amount of cognitive impairment in this population, especially among nursing home residents (Ferrell, Ferrell, & Rivern, 1995).

Pain Assessment

Most pain assessment tools described elsewhere in this guideline are appropriate for use with older people. Herr and Mobily (1993) emphasized the importance of determining the older person's preference for and ability to complete selected tools before use. They noted that older adults found verbal descriptive tools easier to use and preferred them to visual analog scales. Parmelee (1996) reported that older people with cognitive deficits are less inclined to report pain than cognitively intact older persons of similar health status. As the AGS Clinical Practice Guidelines Panel emphasized, even people with mild to moderate cognitive impairment can be assessed with simple questions and screening tools, and the most reliable source of pain measurement is the older person's self-report.

Pharmacologic Management

Adults over the age of 65 commonly have been excluded from studies of analgesic medications (Rochon, Fortin, Dear, Minaker, & Chalmers, 1993). Therefore, much of the knowledge of pain management in the older adult has

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been gained through clinical experience. There is a potential for adverse effects of medications in all populations, but it is particularly problematic in older adults. Ninety-eight percent of the adverse effects of NSAIDs are those associated with the GI tract (Winzeler & Rosenstein, 1998). Older age is a major risk factor for ulcer complication in people who take NSAIDs (Pepper, 2000), and most of the serious complications occur in older and debilitated patients. Age-related changes in prostaglandins may contribute to the higher incidence of NSAID GI complications in older adults, but it likely is related more to the increased exposure to NSAIDs and to comorbid conditions (Solomon & Gurwitz, 1997). Older people also are at increased risk of adverse renal effects from NSAIDs. Therefore, the antiinflammatory and analgesic benefits of NSAIDs should be weighed against the potential risk, particularly in older people.

If nonselective NSAIDs are used in older adults, they should be started in low analgesic doses and increased to full antiinflammatory doses only if lower doses do not provide adequate relief of symptoms. In the person who is at increased risk for a serious upper GI adverse event, gastroprotective agents should be used even if nonselective NSAIDs are given at low dosage (American College of Rheumatology, 2000).

Older people may be more sensitive to the analgesic properties of opioids. Higher peak pain relief and longer duration of action among older adults have been observed for morphine and other opioid medications (Kaiko, Wallenstein, Rogers, Grabinski, & Houde, 1982). As noted repeatedly in this guideline, the management of pain should be individualized to the needs and characteristics of the patient. The content of this guideline is applicable to pain management in older adults, with special attention given to the aspects discussed in this section.

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VI. Summary and Comments

The *Guideline for the Management of Pain in Osteoarthritis, Rheumatoid Arthritis, and Juvenile Chronic Arthritis* is based on the best available scientific evidence combined with the expert judgment of the panel, consultants, and peer reviewers. The guideline includes information on assessment of pain and functioning in children and adults and takes a comprehensive approach to the use of pain management strategies. The algorithms and narrative discussion emphasize the need for a multimodel approach and ongoing assessment and reassessment to provide the most effective pain management.

An examination of the tables of scientific evidence in Chapter II shows that evidence frequently is sparse or inconsistent, particularly for children and older adults. Most of the medication studies have been conducted to gain Food and Drug Administration approval or for marketing purposes. They often are narrowly focused on patient population or condition and do not provide information that is readily generalizable to other clinical populations, ages, and conditions. The extrapolation of experience with medications commonly used in one clinical population to another population requires considerable dependence on the use of expert judgment in making recommendations regarding their use in pain related to arthritis.

Fortunately, there has been an increase in the development of new medications and routes of administration in recent years, and this should increase available options for pain management. As new scientific evidence becomes available it should be possible to expand treatment options, and there likely will be need to modify recommendations. For now, this evidence-based guideline should provide a useful and current framework for the management of pain in osteoarthritis, rheumatoid arthritis, and juvenile chronic arthritis.

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Appendix A. Pain Assessment Instruments**Table 30. Pain Assessment Instruments and Dimensions Assessed**

Instrument	Description	Dimensions Assessed
Numeric Pain Intensity Scale	Person selects a number on a scale that best describes intensity of pain	Intensity
Visual Analog Scales	Usually consists of a 10-cm line with description at endpoints that measures pain or affect Person places mark along line to indicate intensity of pain or affect and this is then measured to determine score	Intensity and affect
Verbal Rating Scale	Consists of series of pain descriptors usually arranged in order from lowest level of pain to the highest. Person selects descriptor that best describes intensity of pain or pain affect (using different scales for each)	Intensity or affect
Body Maps	Outline of human figure. Person shades area(s) where they are experiencing pain. A cognitively impaired person can point to pain sites on their own body	Pain location
Daily Diary Records	Person reports on his or her pain multiple times a day (e.g., morning, noon, evening, bedtime)	Duration and time course
Brief Pain Inventory Short Form (Cleeland & Ryan, 1994)	Numerical scale (1-10) that consists of items for person to rate the location, intensity, interference, and relief of pain	Location, intensity, interference, with functional relief
McGill Pain Questionnaire (Melzack, 1975)	Pain inventory with 6 descriptors for level of pain, a body outline, 9 descriptors of temporal aspects	Location, intensity, quality
Multidimensional Pain Inventory (Kerns, Turk, & Rudy, 1985)	Comprehensive assessment of subjective pain experience composed of three parts and 12 scales that measure subjective, behavioral, and psycho-physiological components	Psychosocial, behavioral axes

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Table 31. Pain Assessment Instruments for Children

Instrument & Author	Description	Age	Dimension Assessed
CHEDPS (McGrath et al., 1985)	Six items: cry, facial expression, verbal complaints, movements, touching, leg movements	1-7 years	Behavioral response
Faces Rating Scale (Wong & Baker, 1988)	Six faces from 0-5; child chooses the face that best describes how he or she is feeling	3 years and older	Pain intensity and affect
Oucher Scale (Beyer, 1988; Beyer, Denyes, & Villarruel, 1992)	Picture scale with six faces and scale from 0-100; child chooses picture that best describes pain at present (available in Caucasian, African American, and Hispanic versions)	3-12 years	Pain intensity
Eland Color Tool (Eland, 1985)	Child marks one of four boxes with color chosen to represent how much pain or hurt he or she has. Body outline colored where it hurts.	4 years and older	Pain intensity
Poker Chip (Hester, 1979)	Four poker chips that represent "pieces of hurt" are aligned horizontally in front of child. Child chooses chip that represents the current hurt.	4-8 years	Pain intensity
Numeric Scale	Select a number that best describes intensity of pain.	5 years and older	Pain intensity
Word Graphic Rating Scale	A line with words to describe pain—child marks along the line to show how much pain	5 years and older	Pain intensity
Visual Analog Scale	A 10-cm line with description of pain at end points; a mark is placed along the line to indicate intensity and is then measured to determine score	5 years and older	Pain intensity
Varni/Thompson Pediatric Pain Questionnaire (Varni, Thompson, & Hanson, 1987)	A self-report and parental report; includes visual analog scales, projective color body map, and list of pain descriptor	5 years and older	Pain intensity and location
FIACC Scale (Merkel, Voepel-Lewis, Shnayevitz, Malviya, 1997)	Five items (face, legs, activity, cry, and consolability) summed for total score (0-10)		

Note: From "Pediatric Pain Assessment," by K.H. Videau, Primary Health Care of Children, J.A. Fox (Ed.), 1987, St. Louis: Mosby. Copyright 1987 by Mosby. Adapted with permission. From Guideline for the Management of Acute and Chronic Pain in Sick-Cell Disease, APS Clinical Practice Guidelines Series, No. 1, by L. J. Benjamin, C.D., Dampier, A.K., Jacox, V., Odesina, D., Phoenix, B., Shipilo, M., Shattard, & M. Tisdell, 1999, Glenview, IL: American Pain Society. Copyright 1999 by the American Pain Society. Adapted with permission.

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Table 32. Pain History for Children

Child Form	Parent Form
Tell me what pain is.	What word(s) does your child use in regard to pain?
Tell me about the hurt you have had before.	Describe the pain experiences your child has had before.
Do you tell others when you hurt? If yes, who?	Does your child tell you or others when he or she is hurting?
What do you do for yourself when you are hurting?	How do you know when your child is in pain?
What do you want others to do for you when you hurt?	How does your child usually react to pain?
What don't you want others to do for you when you hurt?	What do you do for your child when he or she is hurting?
What helps the most to take your hurt away?	What does your child do for him/herself when he or she is hurting?
Is there anything special that you want me to know about you when you hurt? (If yes, have child describe)	What works best to decrease or take away your child's pain?
	Is there anything special that you would like me to know about your child and pain? (If yes, describe)

Note: From "Assessment and Management of Pain in Children" by M.O. Hester & C.S. Barcus, 1986, Pediatrics: Nursing Update, pp. 1, 2-8. Princeton, NJ: Continuing Professional Education Center, Inc. Adapted with permission. From Acute Pain Management: Operative or Medical Procedures and Trauma. Clinical Practice Guideline, AHCPR Publication No. 92-0032. Rockville, MD: Agency for Health Care Policy and Research, Public Health Service, U.S. Department of Health and Human Services.

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Appendix B. Health Status, Function, and Quality of Life Assessment Instruments

Table 33. Health Status, Function, and Quality of Life Assessment Instruments

Instruments and Author	Description	Dimension Assessed
General & Musculoskeletal Assessment		
Medical Outcomes Study Short form 36 (SF-36) (Ware & Sherbourne, 1992)	A 36-item form to measure health status	Function, role limitations, pain
Sickness Impact Profile (SIP) (Bergner et al., 1976)	A 136-item self- or interviewer-administered, behaviorally based, health status questionnaire	Function, psychosocial functioning, and pain
Musculoskeletal Functional Assessment (MFA) (Martin, Engelberg, Agel, Snapp, & Swiontkowski, 1996)	A 101-item self-reported health status instrument	Health status, function
Short Musculoskeletal Functional Assessment (SMFA) (Swiontkowski, Engelberg, Martin, & Agel, 1999)	A 46-item questionnaire	Dysfunction index and bother index
Functional Interference Estimate (Toomey, Mann, Hernandez, & Abashian, 1993)	A six-item self-administered rating scale to determine how much pain interferes with functioning	Pain interference with function
MODEMS™ Musculoskeletal Outcomes Data Evaluation Management System (Sokoloff, 1998)	A program sponsored by the American Academy of Orthopaedic Surgeons and the Council of Musculoskeletal Specialty Societies to develop and implement Quality of Life Health Assessment Instruments*	Function postoperatively
Anatomic Specific Assessment		
Hip Harris Hip Score (Mahomed, Arndt, McGroarty, & Harris, 2001; Soderman & Malchau, 2001)	Clinical evaluation measuring improvement between preop and postop	Health status, function
Merle d'Aubigne Hip Scoring System (Merle D'Aubigne, 1990)	Clinical measurement of function between preop and postop	Health status, function, pain
Knee Hospital for Special Surgery (Binazzi, Soudry, Mestriener, & Insall, 1992)	Knee score—tool for evaluating functional performance, particularly during the postoperative period	Function postop
Knee Society Score (Insall, Dorr, Scott, & Scott, 1989)	Knee Score System rates knee joint and the patient's ability to walk and climb stairs	Function
Foot and Ankle Ankle Osteoarthritis Scale (Domsic & Saltzman, 1998)	Modified foot function index, a visual analog-based scale to assess rheumatoid arthritis foot problems, to measure systems and function in osteoarthritis of ankle joint	Health status, function

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Table 33. (cont.) Health Status, Function, and Quality of Life Assessment Instruments

Instruments and Author	Description	Dimension Assessed
ADFAH Hindfoot, Midfoot, and Forefoot Scores (Kitaoka et al., 1994)	Four rating systems developed by American Orthopaedic Foot and Ankle Society—incorporates subject and object factors into numerical scales to describe function, alignment, and pain	Function, alignment, pain
Western Ontario and McMaster University Osteoarthritis Index (Bellamy, Buchanan, Goldsmith, Campbell, & Stitt, 1988)	Disease-Specific Assessment Self-administered health status measure consisting of 24 questions focused on OA of the hip and/or knee	Health status, function, and pain in osteoarthritis
Arthritis Impact Measurement Scale (Meenan, Gertman, & Mason, 1980)	Combination of previously studied and newly created health status scales	All aspects of osteoarthritis
Arthritis Impact Measurement Scale 2 (Meenan, Mason, Anderson, Guccione, & Kazis, 1992)	Revised and expanded Arthritis Impact Measurement Scale. Three new scales added. 78-item self-administered questionnaire.	All aspects of osteoarthritis
Health Assessment Questionnaire (Fries, Spitz, Kraines, & Holman, 1980)	20 questions in eight categories assess ability and function for common activities. Determines need for assistance in activities of daily living.	Function
Modified Health Assessment Questionnaire (Pincus, Summey, Soraci, Walston, & Hummon, 1983)	Reduced to eight-item questionnaire. modified to determine perceived patient satisfaction and degree of change in need for assistance in activities of daily living.	Function

*Some of these instruments include pain measures.

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Table 34. Function and Quality of Life Assessment Instruments for Children

Tool	Description	Time to Complete	Dimensions Examined
Juvenile Arthritis Functional Assessment Scale (JAFAS) (Lovel, et al., 1989)	Trained observer record of 10 tasks in clinical setting	10 minutes	Physical
Juvenile Arthritis Functional Assessment Report (JAFAR) (Howe, et al., 1991)	Child self-report and parent report questionnaires on 23 activities of daily living	10 minutes	Physical
Childhood Health Assessment Questionnaire (CHAQ) (Singh, Athreya, Fries & Goldsmith, 1994)	Child self-report and parent report questionnaires	15 minutes	Physical
Juvenile Arthritis Quality of Life Questionnaire (JAQQ) (Duffy, Arsenault, Duffy, Paquin & Strawczynski, 1997)	Child self-report and parent report questionnaires	20 minutes	Pain Vision Global assessment Fine motor
Juvenile Arthritis Self-Report Index (JASI) (Wright, Law, Crombie, Goldsmith & Dent, 1994)	Child self-report questionnaire with 100 items	30 minutes	Gross motor Psychosocial Pain Systemic symptoms Self-care
PedsQL™ (Varni, Seid, & Rode, 1999; Smith et al., 2000)	Child self-report and parent report questionnaires	10–15 minutes	Domestic Mobility School functioning Physical Psychosocial Pain School functioning Disease-specific symptoms

Note: From "Functional Measures in Children with Rheumatic Diseases" by K.J. Murray & M.H. Passo, 1995, *Pediatric Clinics of North America*, 42, pp. 1127–1154.

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Appendix C. Glossary

Acupuncture. A procedure in which specific body areas associated with peripheral nerves are pierced with fine needles to produce anesthesia, relieve pain, and promote therapy.

Acute pain. Pain that has a sudden onset and commonly declines over a short time (i.e., days, hours, minutes). Follows injury to the body and generally disappears when the bodily injury heals. It is often, but not always, associated with physical signs of autonomic nervous system activity such as tachycardia, hypertension, diaphoresis, mydriasis, and pallor. (APS, 1999)

Addiction. Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations. It is characterized by behaviors that include one or more of the following: impaired control over medication use, compulsive use, continued use despite harm, and craving (APS, AAPM, & ASAM, 2001).

Adjuvant analgesic medication. A medication that is not a primary analgesic but rather a medication that research has shown to have independent or additive analgesic properties (e.g., antidepressant, anticonvulsant).

Arthritis. A generic term that describes more than 100 different conditions. A disorder of a joint where two bones meet, which may be manifested on physical examination by swelling, redness, warmth, or tenderness in the joint or may be demonstrated on radiograph by loss of the joint space, formation of spurs, erosions, or cysts in the bone.

Arthrocentesis. A procedure in which a needle is inserted into the joint to either drain fluid for diagnostic purposes or to inject medications or other materials into the joint.

Arthrodesis. The surgical removal of articular joint surfaces with fixation of bone ends. After bony union, the two bones function as one and there is no motion at the prior joint.

Arthroplasty. Implantation of a prosthesis in a joint.

Arthroscopy. The insertion of an endoscope within a joint. Surgical procedures are then percutaneously performed, guided by visualization through the arthroscope. It may be used for diagnostic evaluations as well as treatments.

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Best evidence synthesis. Evidence based on the best evidence principle as used in law, in which the same evidence that would be essential in one case might be disregarded in a second case because better evidence is available.

Biologic agents. A new category of therapy in rheumatic diseases involving the synthesis of substances that interfere with the basic biologic mechanisms of the disease process. These agents interrupt the natural cascade of events that occur in a particular disease. They may work in part by binding to various biologic messengers that are produced in disease states, or may block receptor sites where these messengers attach to induce further disease.

Body mass index (BMI). A measure of fitness and health that takes both weight and height into account. To calculate BMI, (a) multiply weight (in pounds) by 704.5, (b) square height (in inches), then (c) divide number from Step a by number from Step b.

Breakthrough pain. Intermittent exacerbations of pain that can occur spontaneously or in relation to specific activity; pain that increases above the level of pain addressed by the ongoing analgesics; includes incident pain and end-of-dose failure.

Case study design. A nonexperimental study that extensively explores a single unit (a unit may be a person, family, or group) or a very small number of units.

Catastrophize. The tendency to ruminate upon, focus on, and worry about pain and to evaluate one's ability to control pain in an overly negative fashion.

Chronic pain (nonmalignant). Generally considered to be pain that lasts more than 6 months, is ongoing, is due to non-life-threatening causes, has not responded to current available treatment methods, and may continue for the remainder of the person's life. (Wall & Melzack, 1999)

Combination therapy. Method of treating disease through the simultaneous use of a variety of medications to eliminate or control the biochemical cause of the disease.

Condylectomy. The removal of a condyle, which is a prominent part of the bone at a joint and which may cause a pressure area, particularly in the foot.

Conscious sedation. "Light sedation" during which the patient retains airway reflexes and responds to verbal stimuli.

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Constitutive. Normally present.

Counterirritant. An agent that is applied to produce irritation at one site so as to decrease perception of pain at the same or a distant site.

Counterstimulant. Application of moderate to intense sensory stimulation, such as cold, heat, rubbing, pressure, or electrical current, so as to decrease perception of pain at the same or a distant site.

Cyclooxygenase. Refers to a particular enzyme involved in the formation of prostaglandins in the body. These may be important in the natural physiology in a particular organ or cell, or may be involved in the formation of prostaglandins that induce inflammation in a joint, in which case it may be detrimental.

Cyclooxygenase-1 (COX-1). Is normally present in the body for physiologic reasons. It is also called "constitutive" cyclooxygenase. COX-1 is produced physiologically in the stomach and is protective for the lining of the stomach.

Cyclooxygenase-2 (COX-2). The "inducible" form of cyclooxygenase that arises with joint inflammation and is involved in the diseases of the joints. COX-2 is produced in the joint when "induced" by inflammation.

Descriptive study. A nonexperimental study in which variables or subject characteristics are examined as they naturally occur for the purpose of describing or comparing samples or examining relationships among a set of variables.

Eutectic mixture of local anesthetic (EMLA). An ointment that contains local anesthetics so that topical application causes local anesthesia without the need for injection.

Equianalgesic. Having equal analgesic effect; morphine sulfate (10 mg) parenterally generally is used for opioid analgesic comparisons.

Exostectomy. The removal of a fragment of bone.

Experimental study (randomized controlled trial [RCT]). An experiment that uses random assignment to create treatment and control groups so that changes can be inferred or attributed to the experimental treatment.

Goniometer. An instrument for measuring angles (as of a joint).

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Hyaluronic acid. A substance in the synovial fluid that is responsible for the viscosity of joint fluid. It is important in the lubrication process and in the protection of the joint and allows for smoother motion of the joint.

Hyperalgesia/allodynia. Increased sensitivity to pain or enhanced intensity of pain sensation.

Imagery. A pain relief technique that uses mental images produced by memory or imagination for relaxation or for distraction, depending on the content of the imagery.

Inducible. Able to initiate or increase the production of an enzyme or other protein at the level of genetic transcription; produced in the joint by inflammation.

Incident pain. A type of breakthrough pain that is related to specific activity, such as eating, defecating, socializing, or walking; also referred to as movement pain.

Juvenile chronic arthritis. A group of systemic inflammatory disorders affecting children younger than 16 years of age. Three major subsets are described: (a) pauciarticular onset—four joints or less involved, (b) polyarticular onset—more than four joints involved and (c) systemic onset—with fever, rash, and arthritis.

Loading dose. The initial dose of medication administered for a pain episode.

Maintenance dose. The medication dosage required to produce a given level of analgesia.

Meta-analysis. The process of combining the results of several related studies to obtain more reliable conclusions.

Mixed opioid agonist-antagonist. A compound that has an affinity for two or more types of opioid receptors and blocks opioid effects on one receptor type while producing opioid effects on a second receptor type.

Neuropathic pain. Pain that results from a disturbance of function or pathologic change in a nerve; in one nerve mononeuropathy; in several nerves, mononeuropathy multiplex; if diffuse and bilateral, polyneuropathy.

Nociception. The process of pain transmission; usually relating to a receptive neuron for painful sensations.

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Nociceptive pain. Pain resulting from actual or potential tissue damage; pain resulting from the ongoing activation of primary afferent neurons by noxious stimuli. (The nervous system is intact.)

Nonsteroidal antiinflammatory drug (NSAID). Aspirin-like medication that reduces inflammation (and hence pain) arising from injured tissue.

COX-2 selective NSAID: An NSAID that inhibits the COX-2 isoform of cyclooxygenase, but not the COX-1 form.

Nonselective NSAID: An NSAID that inhibits both COX-1 and COX-2 isoforms of cyclooxygenase.

Number needed to treat (NNT) to prevent one additional adverse outcome. A number which gives an estimate of how many people need to receive a treatment before one person would experience the beneficial outcome (e.g., if you need to give a stroke prevention drug to 20 people before one stroke is prevented, then the NNT for that stroke prevention drug is 20).

Opiate receptor. Opiate-binding sites found throughout primary afferents and the neuraxis.

Opioid. A morphine-like medication that produces pain relief. Preferred to the term "narcotic"; refers to natural, semisynthetic, and synthetic medications that relieve pain by binding to opioid receptors in the nervous system. The term "opioid" is preferred to the term "opiate" because it includes all agonists and antagonists with morphine-like activity, as well as naturally occurring and synthetic opioid peptides.

Opioid agonist. Any morphine-like compound that produces bodily effects including pain relief, sedation, constipation, and respiratory depression.

Opioid agonist-antagonist. A medication that acts as an agonist at one type of opioid receptor, and as an antagonist at another receptor.

Opioid partial agonist. A compound that has an affinity for and stimulates physiological activity at the same cell receptors as opioid agonists but that produces only a partial (i.e., submaximal) bodily response.

Osteoarthritis (OA). A disease of the cartilage that progressively produces a local tissue response, mechanical change, and failure of function. The disease typically affects weight-bearing joints asymmetrically. It is the most common form of arthritis.

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Osteotomy. The sectioning or cutting of bone. This may be used to change angular alignment of a joint surface to relieve diseased areas of weight-bearing stress.

Pain. An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. (IASP) Pain is always subjective.

Pain affect. The affective unpleasantness and emotional arousal caused by pain.

Pain threshold level. The level of intensity at which pain becomes appreciable or perceptible.

Peer review. Evaluation of a guideline by an interdisciplinary panel of experts using the Institute of Medicine (Field & Lohr, 1992) attributes of good clinical practice guidelines as evaluation criteria.

Phalangectomy. The partial or complete removal of the phalanges (i.e., bones of the fingers and toes). This aids in correction of deformities and relief of pressure areas.

Physical dependence. A state of adaptation that is manifested by a medication class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the medication, and/or administration of an antagonist (APS, AAFM, & ASAM, 2001).

Physical modalities. Physical methods such as heat, cold, massage, or exercise used to relieve pain.

Polyarthritis. Refers to inflammation in multiple joints.

Pseudoaddiction. Pattern of medication-seeking behavior of patients receiving inadequate pain management that can be mistaken for addiction.

Quasi-experimental study (includes nonrandomized clinical trial). A design that does not use random assignment to create treatment and control groups but uses other methods to control validity threats so that changes can be inferred or attributed to the experimental treatment.

Randomized controlled trial (RCT). See "experimental study."

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Rescue dose. A bolus or extra dose of medication given as needed (p.r.n.) to relieve pain that breaks through despite a regimen of medication that is given at regularly scheduled intervals.

Rheumatoid arthritis (RA). A chronic inflammatory condition in which the body's immune system attacks cartilage, bone, and sometimes internal organs, usually causing joint disease. Joints become inflamed which leads to swelling, pain, stiffness, and the possible loss of function. It is characterized by a symmetrical pattern of synovitis of the joints leading to progressive destruction.

Subtalar joint. The major point in the hindfoot beneath the ankle. This joint allows eversion and inversion of the foot in concert with the midfoot articulation (talonavicular and calcaneocuboid joints).

Synovitis. Inflammation of the synovial lining tissue of the joint as is seen in inflammatory arthritis.

Taper or wean. A process in which a medication is gradually withdrawn from a patient who is physically dependent on the medication.

Titration. Adjusting the amount (e.g., adjusting the dose of an opioid).

Titration to relief. A gradual increase in pain medication until the highest pain relief is obtained, making the pain as tolerable as possible while minimizing short- and long-term negative effects.

Tolerance. A state of adaptation in which exposure to a medication induces changes that result in a diminution of one or more of the medication's effects over time (APS, AAPM, & ASAM, 2001).

Transcutaneous electrical nerve stimulation (TENS). A method of producing electroanalgesia through electrodes applied to the skin.

Tumor necrosis factor (TNF). Important immune mediator that may be involved in the mechanisms contributing to disease in rheumatoid arthritis. The ability to block TNF with recent biologic agents has helped in control of active disease in patients with rheumatoid arthritis.

Viscosupplementation. A procedure currently approved for use in osteoarthritis in which viscous fluid is injected into a joint (currently the knee joint), which results in decreased pain and increased mobility.

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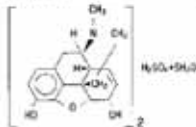
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MS CONTIN is a controlled-release tablet containing morphine sulfate. Following oral administration of a given dose of morphine, the amount systemically absorbed is approximately the same whether the source is MS CONTIN or a conventional formulation. Morphine is released from MS CONTIN somewhat more slowly than from conventional oral preparations, because of its system's elimination (i.e., metabolism in the gut wall and liver) only about 40% of the administered dose reaches the central compartment.

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, stomach, heart, lungs, spleen, and brain. Morphine also crosses the placental membrane and has been found in breast milk.

Although a small fraction (less than 5%) of morphine is converted to its glucuronide metabolites, among these, morphine-3-glucuronide is present in the highest plasma concentration following oral administration.

The glucuronide system has a very high capacity and is not easily saturated even in disease. Therefore, rate of delivery of morphine to the gut and liver should not influence the rate and quantity of the active moieties of the various metabolites formed. Moreover, even if rate affected the relative amounts of each metabolite formed, it should be unimportant clinically because morphine and metabolites are primarily inactive.

The following pharmacokinetic parameters show considerable inter-subject variation but are representative of average values reported in the literature. The volume of distribution (V_D) for morphine is 4 liters per kilogram, and its terminal elimination half-life is normal (3 to 4 hours).

Following the administration of conventional oral morphine products, approximately 50% percent of the morphine that will reach the central compartment, is metabolized within 30 minutes. Following the administration of an equal amount of MS CONTIN to normal volunteers, however, this extent of absorption occurs, on average, after 1.5 hours.

The possible effect of food upon the systemic bioavailability of MS CONTIN has not been systematically evaluated for all strengths. Data from at least one study suggests that food may not alter the bioavailability of MS CONTIN with a daily meal may cause a slight decrease in peak plasma concentration.

Variation in the physicochemical properties of a formulation of an oral morphine drug product can affect its in vivo bioavailability and its absorption rate constant (k_a). The formulation evaluated in MS CONTIN has not been shown to affect morphine's oral bioavailability, but does decrease its apparent *t_{1/2}* (other than pharmacokinetic parameters *t_{1/2}*, volume of distribution (V_D), elimination rate constant (k_e), clearance (CL), are unchanged as they are fundamental properties of morphine in the organism, however, in chronic use, the possibility that shifts in metabolism to parent drug ratios may occur cannot be excluded. When immediate-release oral morphine or MS CONTIN is given as a fixed dosing regimen, steady-state is reached in about a day.

For a given dose and dosing interval, the AUC and average blood concentration of morphine at steady state (C_{ss}) will be independent of the dosing rate of oral formulation administered so long as the formulation have the same absolute bioavailability. The absorption rate of a formulation will, however, affect the mean time (T_{max}) and maximum (C_{max}) blood levels and the times of their occurrence.

Pharmacodynamics

The effects described below are common to all morphine-containing products.

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation

(i.e., sleepiness and anorexia).

The precise mechanism of the analgesic action is unknown. However, specific CNS opiate receptors and endogenous components with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of a variety of effects.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension, and to chemical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine also causes miosis, even in total darkness. Pinpoint pupils are a sign of overdose when the pupils do not respond to 1% pilocarpine. In the absence of pupillary dilation, a patient may be overdosed. Marked mydriasis rather than miosis may be seen in a worsening hypoxia.

Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary, and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the smooth muscle of the stomach and duodenum. Digestion of food in the small intestine is delayed and peptic secretions are decreased. Peristaltic waves in the colon are decreased, while tone is increased in the rectum. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of sphincter of Oddi.

Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to vasodilation-induced hypotension. Manifestations of histamine release, and/or peripheral vasodilation may include flushing, laryngitis, and sweating.

Plasma Levels—Analgesia Relationships

In any particular patient, both analgesic effects and plasma morphine concentrations are related to the morphine dose. In non-tolerant individuals, plasma morphine concentrations of 500 ng/mL have been demonstrated and suggest that plasma concentrations occur after oral administration, leading to a 4- to 6-hour, or longer, between oral changes in plasma morphine concentrations and the effects of such changes. The most direct and predictable concentration-effect relationships can, therefore, be expected at distribution equilibrium and/or steady-state conditions. In general, the minimum effective analgesic concentration in the plasma of non-tolerant patients ranges from approximately 5 to 20 ng/mL.

While plasma morphine effect relationships can be demonstrated in non-tolerant individuals, they are influenced by a wide variety of factors and are not generally useful as a guide to the clinical use of morphine. The effective dose in opioid-tolerant patients may be 10-50 times as great (or greater) than the appropriate dose for non-tolerant individuals. Dosages of morphine should be adjusted and must be titrated to the desired clinical objectives of the patient and the source between therapeutic and adverse effects.

For any fixed dose and dosing interval, MS CONTIN will have a steady-state, a lower C_{max} and a higher C_{min} than conventional morphine. This is a potential advantage: a reduced fluctuation in morphine concentration during the dosing interval should keep morphine blood levels more constant under the theoretical "therapeutic window" of tolerance for a dosing interval as defined as (C_{max}/C_{min}) (C_{max}/C_{min}) (C_{max}/C_{min}). On the other hand, the degree of fluctuation in blood morphine concentration might conceivably affect other phenomena. For example, reduced fluctuations in blood morphine concentrations might influence the rate of tolerance induction.

The elimination of morphine occurs primarily as renal excretion of 3-morphine glucuronide. A small amount of morphine is excreted in the bile, and there is some release into breast milk. Because morphine is primarily metabolized to inactive moieties, the effects of renal disease on morphine's elimination are not likely to be pronounced. However, as with any drug, caution should be taken to guard against unimportant accumulation if renal and/or hepatic function is seriously impaired.

INDICATIONS AND USAGE

MS CONTIN is a controlled-release oral morphine formulation indicated for the relief of moderate to severe pain. It is intended for use in patients who require repeated dosing with potent opioid analgesics over periods of more than a few days.

The MS CONTIN 200 mg tablet is a high dose, controlled-release, oral morphine formulation indicated for the relief of pain in opioid-tolerant patients only.

CONTRAINDICATIONS

MS CONTIN is contraindicated in patients with known hypersensitivity to the drug, in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe block of airways.

MS CONTIN is contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS (See also CLINICAL PHARMACOLOGY)

Impaired Respiration

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in the elderly and debilitated patients as well as in those suffering from opioid use accompanied by hypoxia or hyperventilation when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in others having a substantially depressed respiratory reserve, hypoxia, hyperventilation, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine plus carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or pre-existing increases in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increases in pressure in patients with head injury.

Hypotension Effect

MS CONTIN, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain a blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines or general anesthetics. (See also: PRECAUTIONS, Drug Interactions.) MS CONTIN may produce orthostatic hypotension in ambulatory patients.

MS CONTIN, like all opioid analgesics, should be administered with caution to patients in circulation shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Interactions with other CNS Depressants

MS CONTIN, like all opioid analgesics, should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers, and alcohol because respiratory depression, hypotension, and profound sedation or coma may result.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

From a theoretical perspective, agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, buprenorphine, and butorphanol) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure agonist opioid analgesic. In these patients, mixed agonist/antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

Drug Dependence

Morphine can produce drug dependence and has a potential for being abused. Tolerance as well as psychological and physical dependence may develop upon repeated administration. Physical dependence, however, is not of paramount importance in the management of terminal or palliative patients in severe pain. Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. After prolonged exposure to opioid analgesics, if withdrawal is necessary, it must be undertaken gradually. (See DRUG ABUSE AND DEPENDENCE.)

Infants born to mothers physically dependent on opioid analgesics may also be physically dependent and exhibit respiratory depression and withdrawal symptoms. (See DRUG ABUSE AND DEPENDENCE.)

Other

Although not strictly rare, cases of anaphylaxis have been reported.

PRECAUTIONS (See also CLINICAL PHARMACOLOGY)

Special precautions regarding MS CONTIN 200 mg Tablets

MS CONTIN 200 mg Tablets are for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. Care should be taken in its prescription and patients should be instructed against use by individuals other than the patient for whom it was prescribed, as this may have severe medical consequences for that individual.

General

MS CONTIN is intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The controlled-release nature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See CLINICAL PHARMACOLOGY, Pharmacokinetics and Metabolism.) However, MS CONTIN does not release morphine continuously over the course of a dosing interval. The administration of single doses of MS CONTIN on a q12h dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations on a q4h regimen. The clinical significance of plasma fluctuations in morphine levels has not been systematically evaluated. (See DOSAGE AND ADMINISTRATION.)

As with any potent opioid, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to ensure for every consideration that is important to the selection of the initial dose and dosing interval of MS CONTIN, patients should be given to 1) the daily dose, potency, and characteristics of the agent; 2) whether it has been used previously (i.e., whether it is a pure agonist or mixed agonist/antagonist); 3) the reliability of the relative potency estimate used to calculate the dose of morphine needed (N.B. potency estimates may vary with the route of administration); 4) the degree of opioid tolerance, if any; and 5) the general condition and medical status of the patient.

Selection of patients for treatment with MS CONTIN should be governed by the same principles that apply to the use of morphine or other potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; hyperventilation or hyperventilation-induced alkalosis (e.g., Addison's Disease); CNS depression or coma; toxic infections; prostatic hypertrophy; or urethral stricture; acute bronchitis; chronic bronchitis; hypotension; or inability to swallow.

The administration of morphine like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Morphine may aggravate pre-existing conditions in patients with convulsive disorders. Morphine should be used with caution in patients about to undergo surgery or the biliary tract since it may cause spasm of the sphincter of Oddi. Similarly, morphine should be used with caution in patients with acute pancreatitis secondary to biliary tract disease.

Information for Patients

It is clinically advisable, patients receiving MS CONTIN should be given the following instructions by the physician:

1. As morphine pain management entails changes in the dose to maintain best pain control, Patients should be advised of the need to contact their physician if pain control is inadequate, but not to change the dose of MS CONTIN without consulting their physician.
2. Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery). Patients treated with MS CONTIN or whose dose has been changed should refrain from dangerous activity until it is established that they are not adversely affected.
3. Morphine should not be taken with alcohol or other CNS depressants (sedatives, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other prescription medications are currently being used or are prescribed for future use.
4. For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted regarding analgesics and other drug use.
5. Upon completion of therapy, it may be appropriate to taper the morphine dose, rather than abruptly discontinue it.
6. While psychological dependence ("addiction") to morphine used in the treatment of pain is very rare, morphine is one of a class of drugs known to be abused and should be handled accordingly.
7. The MS CONTIN 200 mg Tablet is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. Special care must be taken to avoid accidental ingestion or the use by individuals (including children) other than the patient for whom it was originally prescribed, as such inappropriate use may have severe, even fatal, consequences.

Drug Interactions (See also WARNINGS)

The concurrent use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers, and alcohol may produce additive depressant effects. Respiratory depression, hypotension, and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including MS CONTIN, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Studies of morphine in mice or animals to evaluate the drug's carcinogenic or mutagenic potential in the effect on fertility have not been conducted.

Pregnancy

Teratogenic Effects: CATEGORY C

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NON-CONFIDENTIAL

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Adults with asthma studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women. But marketing experience does not include any adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience cannot exclude the possibility of subsequent in utero damage to the human fetus.

MS CONTIN should be used in pregnant women only when clearly needed. See also **PRECAUTIONS: Labor and Delivery**, and **DRUG ABUSE AND DEPENDENCE**.

Neonatal Effects: Infants born to mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

Labor and Delivery

MS CONTIN is not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the uterine contractions, and frequency of uterine contractions. However, this effect is not considered to be of clinical importance unless the use of an analgesic which tends to shorten labor.

Women whose infants received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific neonatal antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

Nursing Mothers

Low levels of morphine have been detected in the breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped abruptly. Nursing should not be undertaken while a patient is receiving **MS CONTIN** since morphine may be excreted in the milk.

Pediatric Use

Use of **MS CONTIN** has not been evaluated systematically in children.

Geriatric Use

Clinical studies of **MS CONTIN** did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the low end of the dosing range, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression, respiratory arrest, shock, and cardiac arrest.

Most Frequently Observed

Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dyspnea, and euphoria.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some adverse reactions of ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed Reactions

Central Nervous System: Headaches, headache, apnea, tremor, uncontrolled muscle movements, ataxia, ataxias of mood (irritability, apprehension, depression, feeling nervous), drowsiness, muscle rigidity, reduced hallucinations and disorientation, visual disturbances, insomnia, increased intracranial pressure. **Gastrointestinal:** Dry mouth, bitter taste, epigastric burning, anorexia, constipation, taste alteration, constipation, flatulence, intestinal obstruction. **Cardiovascular:** Flushing of the face, dizziness, bradycardia, palpitation, tachycardia, hypotension, hypertension. **Genitourinary:** Urine retention or incontinence, reduced libido and/or potency. **Dermatologic:** Pruritus, urticaria, other skin rashes, edema, diaphoresis. **Other:** Anisocoria, effect of perspiration, muscle tremor, blurred vision, myalgias, clonus, miosis, anisocoria.

DRUG ABUSE AND DEPENDENCE

Opioid analgesics may cause psychological and physical dependence (see **WARNINGS**). Physical dependence results in withdrawal symptoms in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with narcotic antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, etc.). See also **OVERDOSAGE**.

Physical dependence usually does not occur in a clinically significant degree until after several weeks of continued narcotic usage. Tolerance, in which progressively larger doses are required to produce the same degree of analgesia, is initially manifested by a shortened duration of analgesic effect, and ultimately by decreases in the intensity of analgesia.

In chronic-pain patients, and in non-chronic cancer patients, the administration of **MS CONTIN** should be guided by the degree of tolerance "acquired." Physical dependence, per se, is not ordinarily a concern when one is dealing with opioid-tolerant patients whose pain and suffering is associated with an irreversible illness.

If **MS CONTIN** is abruptly discontinued, a moderate to severe abstinence syndrome may occur. The opioid abstinence syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, gooseflesh, restless sleep or "jitters" and myalgias during the first 24 hours. These symptoms often develop in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, headache and aching of muscles, kicking movements, severe lacrimation, abdominal and leg aches, abdominal and muscle cramps, hot and cold flashes, insomnia, nausea, anorexia, vomiting, intestinal spasm, diarrhea, chills and repetitive shivering, increase in body temperature, blood pressure, respiratory rate and heart rate, decrease of systolic blood pressure, loss of fluids through sweating, vomiting and diarrhea. There is usually marked weight loss, dehydration, anorexia, and disturbances in acid-base balance. Cardiovascular collapse can occur. Without treatment mild abstinence symptoms disappear in 5-14 days; however, these appear to be a phase of secondary or chronic abstinence which may last for 2-6 months characterized by irritability, instability, and muscular aches.

If treatment of physical dependence of patients on **MS CONTIN** is necessary, the patient may be detoxified by gradual reduction of the dosage. Gastrointestinal disturbances in detoxification should be treated accordingly.

OVERDOSAGE

Acute overdosage with morphine is manifested by respiratory depression, somnolence progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, bradycardia, hypotension and death.

In the treatment of overdosage, priority attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonist, naloxone, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2.0 mg) should be administered intravenously. However, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is fully re-established. If the response to naloxone is suboptimal or not

sustained, additional naloxone may be administered, as needed, in 2-mg increments intravenously to maintain airway and respiratory function. However, there is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on **MS CONTIN**. In such cases, an abrupt or complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

Note: In an individual physically dependent on opioid, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of a narcotic antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in the physically dependent person, the antagonist should be administered with care and by fraction with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, resuscitation) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or defibrillation.

DOSEAGE AND ADMINISTRATION

(See also **CLINICAL PHARMACOLOGY, WARNINGS, AND PRECAUTIONS** sections.)

MS CONTIN TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE

BROKEN, CHWED, OR CRUSHED.

TAKING BROKEN, CHWED, OR CRUSHED MS CONTIN TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

MS CONTIN is intended for use in patients who require more than several days continuous treatment with a potent opioid analgesic. The controlled-release feature of the formulation allows it to be administered on a more convenient schedule than conventional immediate-release oral morphine products. (See **CLINICAL PHARMACOLOGY: Pharmacokinetics and Metabolism**.) However, **MS CONTIN** does not release morphine continuously over the course of a dosing interval. The administration of single doses of **MS CONTIN** on a 12-hour dosing schedule will result in higher peak and lower trough plasma levels than those that occur when an identical daily dose of morphine is administered using conventional oral formulations in a qid regimen. The clinical significance of greater fluctuations in morphine plasma level has not been systematically evaluated.

As with any potent opioid drug product, it is critical to adjust the dosing regimen for each patient individually, taking into account the patient's prior analgesic treatment experience. Although it is clearly impossible to reevaluate every consideration that is important to the selection of initial dose and dosing interval of **MS CONTIN**, at least should be given to: 1) the daily dose, potency, and precise pharmacokinetics of the opioid the patient has been taking previously (i.e., whether it is a pure agonist or mixed agonist/antagonist); 2) the reliability of the relative potency estimate used to calculate the dose of morphine needed (N.B. potency estimates may vary with the route of administration); 3) the degree of opioid tolerance; 4) any and all the general condition and medical status of the patient.

The following dosing recommendations, therefore, can only be considered suggestive approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient.

Conversion from Conventional Oral Morphine to MS CONTIN

A patient's daily morphine requirement using immediate-release oral morphine (totaling every 4 to 6 hours). The patient is then converted to **MS CONTIN** in either of two ways: 1) by administering one-half of the patient's 24-hour requirement as **MS CONTIN** on an every 12-hour schedule, or 2) by administering one-third of the patient's daily requirement as **MS CONTIN** on an every eight-hour schedule. With either method, dose and dosing intervals are then adjusted as needed (see discussion below). The 15 mg tablet should be used for initial conversion for patients whose oral daily requirement is expected to be less than 60 mg. The 30 mg tablet strength is recommended for patients with a daily morphine requirement of 60 to 120 mg, when the total daily dose is expected to be greater than 120 mg, the appropriate combination of tablet strengths should be employed.

Conversion from Parenteral Morphine or Other Opioids (Parenteral or Oral) to MS CONTIN

MS CONTIN can be administered the initial oral morphine drug product, in this case, however, particular care must be exercised in the conversion process. Because of uncertainty about, and interpatient variation in, relative estimates of opioid potency and more variable initial dosing regimens should be conservative. But, in an underestimation of the 24-hour oral morphine requirement is preferred to an overestimation. To this end, initial individual doses of **MS CONTIN** should be estimated conservatively in patients whose daily morphine requirements are expected to be less than or equal to 120 mg per day. The 30 mg tablet strength is recommended for the initial conversion period. Once a stable dose regimen is reached, the patient can be converted to the 60 mg or 120 mg tablet strength, or an appropriate combination of tablet strengths, if desired.

Estimates of the relative potency of opioids are only approximate and are influenced by route of administration, individual patient differences, and potency by an individual's medical condition. Consequently, it is difficult to recommend any fixed rule for converting a patient to **MS CONTIN** directly. The following general points should be considered, however:

1. **Parenteral to oral morphine only:** Estimates of the oral to parenteral potency of morphine vary. Some authorities suggest that a dose of oral morphine only three times the daily parenteral morphine requirement may be sufficient to obtain a desired effect.
2. **Other parenteral or oral opioids to oral morphine:** Because there is lack of adequate evidence bearing on these types of analgesic substitutions, specific recommendations are not possible.

Physicians are advised to refer to published relative potency data, keeping in mind that such ratios are only approximate. In general, it is safer to underestimate the daily dose of **MS CONTIN** required and rely upon ad hoc supplementation to deal with inadequate analgesia. (See discussion which follows.)

Use of MS CONTIN as the First Dosed Analgesic

There has been no systematic evaluation of **MS CONTIN** as an initial opioid analgesic in the management of pain. Because it may be more difficult to break a patient using a controlled-release morphine, it is ordinarily advisable to begin treatment using an immediate-release formulation.

Considerations in the Adjustment of Dosing Regimens

Whenever the approach, if signs of excessive opioid effects are observed early in a dosing interval, the next dose should be reduced. If this adjustment leads to inadequate analgesia, that is, "breakthrough" pain occurs late in the dosing interval, the dosing interval may be shortened. Alternatively, a supplemental dose of a short-acting analgesic may be given. As experience is gained, adjustments can be made to obtain an appropriate balance between pain relief, opioid side effects, and the convenience of the dosing schedule.

In adjusting dosing requirements, it is recommended that the dosing interval never be extended beyond 12 hours because the administration of very large single doses may lead to acute overdose. (N.B. **MS CONTIN** is a controlled-release formulation; it does not release morphine continuously over the dosing interval.) For patients with low daily morphine requirements, the 15 mg tablet should be used.

Special Instructions for MS CONTIN 200 mg Tablets

(For use in opioid-tolerant patients only.)

The **MS CONTIN 200 mg tablet** is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. It is recommended that this strength be reserved for patients that have already been titrated to a stable analgesic regimen using lower strengths of **MS CONTIN** or other opioids.

Conversion from MS CONTIN to Parenteral Opioids

When converting a patient from **MS CONTIN** to parenteral opioids, it is best to assume that the patient's oral potency is high. NCBI THAT THIS IS THE CONVERSION OF THE STRATEGY USED WHEN THE CONVERSION OF CONVERSION IS FROM THE PARENTERAL TO ORAL FORMULATIONS. IN BOTH CASES, HOWEVER, THE NEW IS TO ESTIMATE THE NEW DOSE CONSERVATIVELY. For example, to estimate the required 24-hour dose of morphine for IM use, one could employ a conversion of 1 mg of morphine IM for every 6 mg of morphine as **MS CONTIN**. Of course, the IM 24-hour dose would have to be divided by six and administered on a qid regimen. This approach is recommended because it is least likely to cause overdose.

Safety and Handling

MS CONTIN TABLETS ARE TO BE TAKEN WHOLE, AND ARE NOT TO BE BROKEN, CHWED, OR CRUSHED. TAKING BROKEN, CHWED, OR CRUSHED **MS CONTIN** TABLETS COULD LEAD TO THE RAPID RELEASE AND ABSORPTION OF A POTENTIALLY TOXIC DOSE OF MORPHINE.

The **MS CONTIN 200 mg tablet** strength is for use only in opioid-tolerant patients requiring daily morphine equivalent dosages of 400 mg or more. The strength is potentially toxic if accidentally ingested and patients and their families should be instructed to take special care to avoid accidental or intentional ingestion by individuals other than those for whom the medication was originally prescribed.

HOW SUPPLIED

NDC 0034-0514-10: **MS CONTIN** (morphine sulfate controlled-release tablets) 15 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0514-12: **MS CONTIN** (morphine sulfate controlled-release tablets) 15 mg are supplied in opaque plastic bottles containing 120 tablets.

NDC 0034-0514-90: **MS CONTIN** (morphine sulfate controlled-release tablets) 15 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0514-25: **MS CONTIN** (morphine sulfate controlled-release tablets) 15 mg are supplied in unit dose packaging with 25 individually numbered tablets per card, one card per glue end carton.

NDC 0034-0515-50: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 50 tablets.

NDC 0034-0515-10: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0515-12: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 120 tablets.

NDC 0034-0515-90: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0515-25: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in unit dose packaging with 25 individually numbered tablets per card, one card per glue end carton.

NDC 0034-0515-50: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 50 tablets.

NDC 0034-0515-10: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0515-12: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 120 tablets.

NDC 0034-0515-90: **MS CONTIN** (morphine sulfate controlled-release tablets) 30 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0516-25: **MS CONTIN** (morphine sulfate controlled-release tablets) 60 mg are supplied in unit dose packaging with 25 individually numbered tablets per card, one card per glue end carton.

NDC 0034-0516-50: **MS CONTIN** (morphine sulfate controlled-release tablets) 60 mg are supplied in opaque plastic bottles containing 50 tablets.

NDC 0034-0516-10: **MS CONTIN** (morphine sulfate controlled-release tablets) 60 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0516-12: **MS CONTIN** (morphine sulfate controlled-release tablets) 60 mg are supplied in opaque plastic bottles containing 120 tablets.

NDC 0034-0516-90: **MS CONTIN** (morphine sulfate controlled-release tablets) 60 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0517-25: **MS CONTIN** (morphine sulfate controlled-release tablets) 100 mg are supplied in unit dose packaging with 25 individually numbered tablets per card, one card per glue end carton.

NDC 0034-0517-50: **MS CONTIN** (morphine sulfate controlled-release tablets) 100 mg are supplied in opaque plastic bottles containing 50 tablets.

NDC 0034-0517-10: **MS CONTIN** (morphine sulfate controlled-release tablets) 100 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0517-12: **MS CONTIN** (morphine sulfate controlled-release tablets) 100 mg are supplied in opaque plastic bottles containing 120 tablets.

NDC 0034-0517-90: **MS CONTIN** (morphine sulfate controlled-release tablets) 100 mg are supplied in opaque plastic bottles containing 500 tablets.

NDC 0034-0518-25: **MS CONTIN** (morphine sulfate controlled-release tablets) 200 mg are supplied in unit dose packaging with 25 individually numbered tablets per card, one card per glue end carton.

NDC 0034-0518-50: **MS CONTIN** (morphine sulfate controlled-release tablets) 200 mg are supplied in opaque plastic bottles containing 50 tablets.

NDC 0034-0518-10: **MS CONTIN** (morphine sulfate controlled-release tablets) 200 mg are supplied in opaque plastic bottles containing 100 tablets.

NDC 0034-0518-12: **MS CONTIN** (morphine sulfate controlled-release tablets) 200 mg are supplied in opaque plastic bottles containing 120 tablets.

NDC 0034-0518-90: **MS CONTIN** (morphine sulfate controlled-release tablets) 200 mg are supplied in opaque plastic bottles containing 500 tablets.

Store at controlled room temperature: 15°-30°C (59°-86°F).

Dispense in a light, light-resistant container.

CAUTION

Order Form Required.

The Purdue Frederick Company

Stamford, CT 06903-3431

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August 16, 2002 01000019-011 0PM223

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MSIR®
Oral Solution Concentrate*
(morphine sulfate)**WARNING: DRUG CONCENTRATE—**
CHECK DOSAGE AND MEASURE
ACCURATELY.**MSIR®**
Immediate-Release Oral Tablets
(morphine sulfate)**MSIR®**
Immediate-Release Oral Capsules
(morphine sulfate)***This product contains dry natural rubber**
091530-02-001 (003)1M-41-1**DESCRIPTION**Chemically, morphine sulfate is 7,8-didehydro-4,5- α -epoxy-17-methyl-morphinan-3,6- α -diol sulfate (2:1 salt) pentahydrate and has the following structural formula:**MSIR Oral Solution Concentrate**

Each 1 mL of MSIR Oral Solution Concentrate contains:

Morphine Sulfate 20 mg

inactive ingredients: edetate disodium, sodium benzoate, and other ingredients.

MSIR Tablets

Each MSIR Tablet for oral administration contains:

Morphine Sulfate 15 or 30 mg

inactive ingredients: croscarmellose sodium, lactose, magnesium stearate, microcrystalline cellulose and talc.

MSIR Capsules

Each MSIR Capsule for oral administration contains:

Morphine Sulfate 15 or 30 mg

inactive ingredients: FD&C blue No. 1, FD&C blue No. 2, FD&C red No. 40, FD&C yellow No. 6, gelatin, hydroxypropyl methylcellulose, lactose, polyethylene glycol, polyborate 80, polyvinylpyrrolidone, starch, sucrose, titanium dioxide, and other ingredients. In addition, the 30 mg capsule contains black iron oxide and D&C red No. 28.

CLINICAL PHARMACOLOGY**Metabolism and Pharmacokinetics**

MSIR Solution, Tablets, and Capsules containing morphine sulfate are for oral administration and are conventional immediate-release products. Only about 40% of the administered dose reaches the central compartment because of pre-systemic elimination (i.e., metabolism in the gut wall and liver).

Once absorbed, morphine is distributed to skeletal muscle, kidneys, liver, intestinal tract, lungs, spleen, and brain. Morphine also crosses the placental membranes and has been found in breast milk.

Although a small fraction (less than 5%) of morphine is demethylated, for all practical purposes virtually all morphine is converted to glucuronide metabolites; among these, morphine-3-glucuronide is present in the highest plasma concentration following oral administration.

The glucuronide system has a very high capacity and is not easily saturated even in disease. Therefore, rate of delivery of morphine to the gut and liver should not influence the total and, probably, the relative quantities of the various metabolites formed. Moreover, even if rate affected the relative amounts of each metabolite formed, it should be unimportant clinically because morphine's metabolites are ordinarily inactive.

The following pharmacokinetic parameters show considerable intersubject variation but are representative of average values reported in the literature. The volume of distribution (Vd) for morphine is 4 liters per kilogram, and its terminal elimination half-life is approximately 2 to 4 hours. Following the administration of conventional oral morphine products, approximately 50% of the morphine that will reach the central compartment intact reaches it within 30 minutes.

Variation in the physical/mechanical properties of a formulation of an oral morphine drug product can affect both its absolute bioavailability and its absorption rate constant (k_a). The basic pharmacokinetic parameters (e.g., volume of distribution [Vd], elimination rate constant [k_e], clearance [Cl]) are fundamental properties of morphine in the organism. However, in chronic use, the possibility that shifts in metabolism to parent drug ratios may occur cannot be excluded.

When immediate-release oral morphine is given on a fixed dosing regimen, steady-state is achieved in about a day.

For a given dose and dosing interval, the AUC and average blood concentration of morphine at steady-state (C_{ss}) will be independent of the specific type of oral formulation administered so long as the formulations have the same absolute bioavailability. The absorption rate of a formulation will, however, affect the maximum (C_{max}) and minimum (C_{min}) blood levels and the times of their occurrence.

While there is no predictable relationship between morphine blood levels and analgesic response, effective analgesia will not occur below some minimum blood level in a given patient. The minimum effective blood level for analgesia will vary among patients, especially among patients who have been previously treated with potent mu (μ) agonist opioids. Similarly, there is no predictable relationship between blood morphine concentration and unwanted clinical responses; again, however, higher concentrations are more likely to be toxic than lower ones.

The elimination of morphine occurs primarily as renal excretion of 3-morphine glucuronide. A small amount of the glucuronide conjugate is excreted in the bile, and there is some minor enterohepatic recycling.

The elimination half-life of morphine is reported to vary between 2 and 4 hours. Thus, steady-state is usually achieved on most regimens within a day. Because morphine is primarily metabolized to inactive metabolites, the effects of renal disease on morphine's elimination are not likely to be pronounced. However, as with any drug, caution should be taken to guard against unanticipated accumulation if renal and/or hepatic function is seriously impaired.

Individual differences in the metabolism of morphine suggest that MSIR Oral Solution, Tablets, and Capsules be dosed conservatively according to the dosing initiation and titration recommendations in the **DOSAGE AND ADMINISTRATION** section.**PHARMACODYNAMICS**

The effects described below are common to all morphine-containing products.

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis).

The precise mechanism of analgesic action is unknown. However, specific CNS opiate receptors and endogenous compounds with morphine-like activity have been identified throughout the brain and spinal cord and are likely to play a role in the expression of analgesic effects.

Morphine produces respiratory depression by direct action on brain stem respiratory centers. The mechanism of respiratory depression involves a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension, and to electrical stimulation.

Morphine depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pericorneal lesions of hemorrhagic or ischemic origins may produce similar findings). Marked mydriasis rather than miosis may be seen with worsening hypoxia.

Gastrointestinal Tract and Other Smooth Muscle

Gastric, biliary and pancreatic secretions are decreased by morphine. Morphine causes a reduction in motility associated with an increase in tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. In addition, propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm. The end result is constipation. Morphine can cause a marked increase in biliary tract pressure as a result of spasm of the sphincter of Oddi.

Cardiovascular System

Morphine produces peripheral vasodilation which may result in orthostatic hypotension. Release of histamine can occur and may contribute to narcotic-induced hypotension. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, and sweating.

INDICATIONS AND USAGE

MSIR Oral Solution, Tablets, and Capsules are indicated for the relief of moderate to severe pain.

CONTRAINDICATIONS

MSIR Oral Solution, Tablets, and Capsules are contraindicated in patients with known hypersensitivity to the drug, in patients with respiratory depression in the absence of resuscitative equipment, and in patients with acute or severe bronchial asthma.

MSIR Oral Solution, Tablets, and Capsules are contraindicated in any patient who has or is suspected of having a paralytic ileus.

WARNINGS (See also: CLINICAL PHARMACOLOGY)**Impaired Respiration**

Respiratory depression is the chief hazard of all morphine preparations. Respiratory depression occurs most frequently in elderly and debilitated patients, and those suffering from conditions accompanied by hypoxia or hypercapnia when even moderate therapeutic doses may dangerously decrease pulmonary ventilation.

Morphine should be used with extreme caution in patients with chronic obstructive pulmonary disease or cor pulmonale, and in patients having a

substantially decreased respiratory reserve, hypoxia, hypercapnia, or pre-existing respiratory depression. In such patients, even usual therapeutic doses of morphine may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects of morphine with carbon dioxide retention and secondary elevation of cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or pre-existing increase in intracranial pressure. Morphine produces effects which may obscure neurologic signs of further increase in pressure in patients with head injuries.

Hypotensive EffectsMSIR Oral Solution, Tablets, and Capsules, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain his blood pressure has already been compromised by a depleted blood volume, or a concurrent administration of drugs such as phenothiazines, or general anesthetics. (See also: **PRECAUTIONS: Drug Interactions**) MSIR Oral Solution, Tablets, and Capsules may produce orthostatic hypotension in ambulatory patients.

MSIR Oral Solution, Tablets, and Capsules, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Interactions with Other CNS Depressants

MSIR Oral Solution, Tablets, and Capsules, like all opioid analgesics, should be used with great caution and in reduced dosage in patients who are concurrently receiving other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, other tranquilizers and alcohol, because respiratory depression, hypotension and profound sedation or coma may result.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics

From a theoretical perspective, agonist/antagonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should NOT be administered to a patient who has received or is receiving a course of therapy with a pure agonist opioid analgesic. In these patients, mixed agonist-antagonist analgesics may reduce the analgesic effect or may precipitate withdrawal symptoms.

Drug DependenceMorphine can produce drug dependence and has a potential for being abused. Tolerance and psychological and physical dependence may develop upon repeated administration. Physical dependence, however, is not of paramount importance in the management of terminally ill patients or any patient in severe pain. Abrupt cessation or a sudden reduction in dose after prolonged use may result in withdrawal symptoms. After prolonged exposure to opioid analgesics, if withdrawal is necessary, it must be undertaken gradually. (See **DRUG ABUSE AND DEPENDENCE**).Infants born to mothers physically dependent on opioid analgesics may also be physically dependent and exhibit respiratory depression and withdrawal symptoms. (See **DRUG ABUSE AND DEPENDENCE**).**PRECAUTIONS (See also: CLINICAL PHARMACOLOGY)****General**

MSIR Oral Solution, Tablets, and Capsules are intended for use in patients who require a potent opioid analgesic for relief of moderate to severe pain. Selection of patients for treatment with MSIR Oral Solution, Tablets, and Capsules should be governed by the same principles that apply to the use of morphine and other potent opioid analgesics. Specifically, the increased risks associated with its use in the following populations should be considered: the elderly or debilitated and those with severe impairment of hepatic, pulmonary, or renal function; myxedema or hypothyroidism; adrenocortical insufficiency (e.g., Addison's Disease); CNS depression or coma; toxic psychosis; prostatic hypertrophy or urethral stricture; acute alcoholism; delirium tremens; hypovolemia; or inability to swallow.

The administration of morphine, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Morphine may aggravate pre-existing convulsions in patients with convulsive disorders.

Morphine should be used with caution in patients about to undergo surgery of the biliary tract, since it may cause spasm of the sphincter of Oddi. Similarly, morphine should be used with caution in patients with acute pancreatitis secondary to biliary tract disease.

Information for Patients

If clinically advisable, patients receiving MSIR Oral Solution, Tablets, and Capsules should be given the following instructions by the physician.

1. Morphine may produce physical and/or psychological dependence. For this reason, the dose of the drug should not be adjusted without consulting a physician.
2. Morphine may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating machinery).
3. Morphine should not be taken with alcohol or other CNS depressants (sleep aids, tranquilizers) because additive effects including CNS depression may occur. A physician should be consulted if other pro-

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such medications are currently being used or are prescribed for future use.

4. For women of childbearing potential who become or are planning to become pregnant, a physician should be consulted regarding analgesics and other drug use.

Drug Interactions (See also WARNINGS)

The concomitant use of other central nervous system depressants including sedatives or hypnotics, general anesthetics, phenothiazines, tranquilizers and alcohol may produce additive depressant effects. Respiratory depression, hypotension and profound sedation or coma may occur. When such combined therapy is contemplated, the dose of one or both agents should be reduced. Opioid analgesics, including MSIR Oral Solution, Tablets, and Capsules, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Carcinogenicity/Mutagenicity/Impairment of Fertility

Studies of morphine sulfate in animals to evaluate the drug's carcinogenic and mutagenic potential or the effect on fertility have not been conducted.

Pregnancy

Teratogenic effects - Category C: Adequate animal studies on reproduction have not been performed to determine whether morphine affects fertility in males or females. There are no well-controlled studies in women, but marketing experience does not include any evidence of adverse effects on the fetus following routine (short-term) clinical use of morphine sulfate products. Although there is no clearly defined risk, such experience cannot exclude the possibility of infrequent or subtle damage to the human fetus. MSIR Oral Solution, Tablets, and Capsules should be used in pregnant women only when clearly needed. (See also: **PRECAUTIONS: Labor and Delivery** and **DRUG ABUSE AND DEPENDENCE**)

Neonatal effects: Infants born from mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

Labor and Delivery

MSIR Oral Solution, Tablets, and Capsules are not recommended for use in women during and immediately prior to labor. Occasionally, opioid analgesics may prolong labor through actions which temporarily reduce the strength, duration, and frequency of uterine contractions. However, this effect is not consistent and may be offset by an increased rate of cervical dilation which tends to shorten labor.

Neonates whose mothers received opioid analgesics during labor should be observed closely for signs of respiratory depression. A specific narcotic antagonist, naloxone, should be available for reversal of narcotic-induced respiratory depression in the neonate.

Nursing Mothers

Low levels of morphine have been detected in human milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of morphine sulfate is stopped. Nursing should not be undertaken while a patient is receiving MSIR Oral Solution, Tablets, and Capsules since morphine may be excreted in the milk.

Pediatric Use

MSIR Oral Solution, Tablets, and Capsules have not been evaluated systematically in children.

ADVERSE REACTIONS

The adverse reactions caused by morphine are essentially the same as those observed with other opioid analgesics. They include the following major hazards: respiratory depression, apnea, and to a lesser degree, circulatory depression; respiratory arrest, shock, and cardiac arrest.

Most Frequently Observed

Constipation, lightheadedness, dizziness, sedation, nausea, vomiting, sweating, dysphoria, and euphoria.

Some of these effects seem to be more prominent in ambulatory patients and in those not experiencing severe pain. Some adverse reactions in ambulatory patients may be alleviated if the patient lies down.

Less Frequently Observed Reactions

Central Nervous System: Weakness, headache, agitation, tremor, uncoordinated muscle movements, vertigo, alterations of mood (irritability, apathy, depression, floating feelings), dreams, muscle rigidity, transient hallucinations and disorientation, visual disturbances, isomeria and increased intracranial pressure.

Gastrointestinal: Dry mouth, bilious tract spasm, laryngospasm, anorexia, diarrhea, cramps and taste alterations.

Cardiovascular: Flushing of the face, chills, tachycardia, bradycardia, palpitation, faintness, syncope, hypotension and hypertension.

Genitourinary: Urinary retention or hesitancy, reduced libido and/or potency.

Dermatologic: Pruritus, urticaria, other skin rashes, edema and diaphoresis.

Other: Atrial urtic effect, paresthesia, muscle tremor, blurred vision, nystagmus, diplopia and miosis.

DRUG ABUSE AND DEPENDENCE

Opioid analgesics may cause psychological and physical dependence. (See **WARNINGS**). Physical dependence results in withdrawal symptoms

in patients who abruptly discontinue the drug or may be precipitated through the administration of drugs with narcotic antagonist activity, e.g., naloxone or mixed agonist/antagonist analgesics (pentazocine, etc.; see also **OVERDOSAGE**). Physical dependence usually does not occur to a clinically significant degree until after several weeks of continued narcotic usage. Tolerance, in which increasingly large doses are required in order to produce the same degree of analgesia, is usually manifested by a shortened duration of a narcotic effect and, subsequently, by decreases in the intensity of analgesia.

In chronic-pain patients and in narcotic-tolerant cancer patients, the administration of MSIR Oral Solution, Tablets, and Capsules should be guided by the degree of tolerance manifested. Physical dependence, per se, is not ordinarily a concern when one is dealing with opioid-tolerant patients whose pain and suffering is associated with an inoperable illness.

If MSIR Oral Solution, Tablets, and Capsules are abruptly discontinued, a moderate to severe withdrawal syndrome may occur. The opioid antagonist abstinence syndrome is characterized by some or all of the following: restlessness, lacrimation, rhinorrhea, yawning, perspiration, cutaneous pruritus, restless sleep known as the "yawns" and mydriasis during the first 24 hours. These symptoms often increase in severity and over the next 72 hours may be accompanied by increasing irritability, anxiety, weakness, twitching and spasms of muscles; kicking movements; severe backache, abdominal and leg pains; abdominal and muscle cramps; hot and cold flashes; insomnia; nausea, anorexia, vomiting, intestinal spasm, diarrhea, coryza and repetitive sneezing, and increase in body temperature, blood pressure, respiratory rate and heart rate. Because of excessive loss of fluids through sweating, vomiting and diarrhea, there is usually marked weight loss, dehydration, ketosis, and disturbances in acid-base balance. Cardiovascular collapse may occur. Without treatment, most observable symptoms disappear in 5-14 days; however, there appears to be a phase of secondary or chronic abstinence which may last for 2-6 months, characterized by insomnia, irritability, and muscular aches.

If treatment of physical dependence on MSIR Oral Solution, Tablets, and Capsules is necessary, the patient may be detoxified by gradual reduction of the dosage. Gastrointestinal disturbances or dehydration should be treated accordingly.

OVERDOSAGE

Acute overdosage with morphine is manifested by respiratory depression, semiconsciousness progressing to stupor or coma, skeletal muscle flaccidity, cold and clammy skin, constricted pupils, and, sometimes, bradycardia and hypotension.

In the treatment of overdosage, primary attention should be given to the re-establishment of a patent airway and institution of assisted or controlled ventilation. The pure opioid antagonist, naloxone, is a specific antidote against respiratory depression which results from opioid overdose. Naloxone (usually 0.4 to 2.0 mg) should be administered intravenously; however, because its duration of action is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably reestablished. If the response to naloxone is suboptimal or not sustained, additional naloxone may be re-administered, as needed, or given by continuous infusion to maintain alertness and respiratory function. However, there is no information available about the cumulative dose of naloxone that may be safely administered.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known or suspected to be physically dependent on morphine. In such cases, an abrupt or complete reversal of narcotic effects may precipitate an acute abstinence syndrome.

Note: In an individual physically dependent on opioids, administration of the usual dose of the antagonist will precipitate an acute withdrawal syndrome. The severity of the withdrawal syndrome produced will depend on the degree of physical dependence and the dose of the antagonist administered. Use of a narcotic antagonist in such a person should be avoided. If necessary to treat serious respiratory depression in the physically dependent patient the antagonist should be administered with extreme care and by titration with smaller than usual doses of the antagonist.

Supportive measures (including oxygen, vasopressors) should be employed in the management of circulatory shock and pulmonary edema accompanying overdose as indicated. Cardiac arrest or arrhythmias may require cardiac massage or resuscitation.

DOSAGE AND ADMINISTRATION (See also **CLINICAL PHARMACOLOGY, WARNINGS** and **PRECAUTIONS** sections)

WARNING: DRUG CONCENTRATE—CHECK DOSAGE AND MEASURE ACCURATELY

Dosage of morphine is a patient-dependent variable, which must be individualized according to patient metabolism, age and disease state, and also response to morphine. Each patient should be maintained at the lowest dosage level that will produce acceptable analgesia. As the patient's well-being improves after successful relief of moderate to severe pain, periodic reduction of dosage and/or extension of dosing interval should be attempted to minimize exposure to morphine.

Usual Adult Oral Dose: 1 to 30 mg every four (4) hours or as directed by physician. Administered either as MSIR Oral Solution, MSIR Oral Tablets, or MSIR Oral Capsules. For control of pain in terminal illness, it is

recommended that the appropriate dose of MSIR Oral Solution, MSIR Oral Tablets, or MSIR Oral Capsules be given on a regularly scheduled basis every four hours at the minimum dose to achieve acceptable analgesia. If converting a patient from another narcotic to morphine sulfate on the basis of standard equivalence tables, a 1 to 3 ratio of parenteral to oral morphine equivalence is suggested. This ratio is conservative and may underestimate the amount of morphine required. If this is the case, the dose of MSIR Oral Solution, MSIR Oral Tablets, or MSIR Oral Capsules should be gradually increased to achieve acceptable analgesia and tolerable side effects.

Sprinkling Contents of Capsule on Food or Liquids: MSIR Oral Capsules may be carefully opened and the entire beaded contents added to a small amount of cool, soft food, such as applesauce or pudding, or a liquid, such as water or orange juice. The bead-food mixture should be swallowed immediately and not stored for future use.

HOW SUPPLIED:

MSIR (morphine sulfate) Oral Solution Concentrate: (unit-dosed)

20 mg per 1 mL

NDC 0034-0523-01: plastic bottle with child-resistant dropper in 30 mL size

NDC 0034-0523-02: plastic bottle with child-resistant dropper in 120 mL size.

Discard opened bottle of Oral Solution after 90 days. **Protect from light.**

MSIR (morphine sulfate) Tablets:

15 mg round, white scored tablets

NDC 0034-0518-10: opaque plastic bottle containing 100 tablets. Each tablet bears the symbol PF on the scored side and M115 on the other side.

30 mg capsule-shaped, white scored tablets

NDC 0034-0519-10: opaque plastic bottle containing 100 tablets. Each tablet bears the symbol PF on the scored side and M130 on the other side.

MSIR (morphine sulfate) Capsules:

15 mg capsules, white opaque capsule body with blue cap

NDC 0034-1025-10: opaque plastic bottle containing 100 capsules. Each capsule bears the symbols PF MSIR 15 and THIS END UP.

30 mg capsules, gray opaque capsule body with lavender cap

NDC 0034-1026-10: opaque plastic bottle containing 100 capsules. Each capsule bears the symbols PF MSIR 30 and THIS END UP.

Store MSIR Oral Solution, Tablets, and Capsules at controlled room temperature 15° - 30°C (59°-86°F).

CAUTION

DEA Order Form Required.

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Stamford, CT 06901-3431

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July 11, 2002

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OxyIR®

(oxycodone hydrochloride)
Immediate-Release Oral Capsules
5 mg

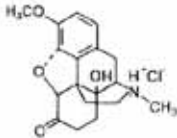
OxyFAST®

(oxycodone hydrochloride)
Immediate-Release
Oral CONCENTRATE Solution*
20 mg/1 mL

*This product contains dry natural rubber. 061430-03-001

DESCRIPTION

Oxycodone is 14-hydroxydihydrocodemone, a white odorless crystalline powder which is derived from the opium alkaloid, thebaine, and may be represented by the following structural formula:



OxyIR® Oral Capsules

Each 5 mg of OxyIR Capsules contains:

Oxycodone hydrochloride 5 mg
Inactive ingredients: Hydroxypropyl methylcellulose, maize starch, polyethylene glycol, polysorbate 80, sucrose, synthetic red iron oxide E172, synthetic yellow iron oxide E172, and titanium dioxide E171.

OxyFAST® Oral CONCENTRATE Solution

Each 1 mL of OxyFAST CONCENTRATE Solution contains:

Oxycodone hydrochloride 20 mg
Inactive ingredients: citric acid, FD&C yellow No. 10, sodium benzoate, sodium citrate, sodium saccharine, and water.

ACTIONS

The analgesic ingredient, oxycodone, is a semisynthetic narcotic with multiple actions qualitatively similar to those of morphine; the most prominent of these involve the central nervous system and organs composed of smooth muscle. The principal actions of therapeutic value of oxycodone are analgesia and sedation.

CLINICAL PHARMACOLOGY

Central Nervous System: Oxycodone is a pure agonist opioid whose principal therapeutic action is analgesia. Other therapeutic effects of oxycodone include anxiolysis, euphoria, and feelings of relaxation. Like all pure opioid agonists, there is no ceiling effect to analgesia, such as is seen with partial agonists or non-opioid analgesics.

The precise mechanism of the analgesic action is unknown. However, specific CNS opioid receptors for endogenous compounds with opioid-like activity have been identified throughout the brain and spinal cord and play a role in the analgesic effects of this drug.

Oxycodone produces respiratory depression by direct action on brain stem respiratory centers. The respiratory depression involves both a reduction in the responsiveness of the brain stem respiratory centers to increases in carbon dioxide tension and to electrical stimulation.

Oxycodone depresses the cough reflex by direct effect on the cough center in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia.

Oxycodone causes miosis, even in total darkness. Pinpoint pupils are a sign of opioid overdose but are not pathognomonic. Marked mydriasis rather than miosis may be seen due to hypoxia in overdose situations.

Gastrointestinal Tract and Other Smooth Muscle: Oxycodone causes a reduction in motility associated

with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone may be increased in the rectum resulting in constipation. Other opioid-induced effects may include a reduction in gastric, biliary, and pancreatic secretions, spasm of sphincter of Oddi, and transient elevations in serum amylase.

Cardiovascular System: Oxycodone may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Concentration—Effect Relationships (PHARMACODYNAMICS): Studies in normal volunteers and patients reveal predictable relationships between oxycodone dosage and plasma oxycodone concentrations, as well as between concentration and certain expected opioid effects. In normal volunteers, these include pupillary constriction, sedation, and overall "drug effect" and in patients, analgesia and feelings of "relaxation." In non-tolerant patients, analgesia is not usually seen at a plasma oxycodone concentration of less than 5-10 ng/mL.

As with all opioids, the minimum effective plasma concentration for analgesia will vary widely among patients, especially among patients who have been previously treated with potent agonist opioids. As a result, patients need to be treated with individualized titration of dosage to the desired effect. The minimum effective analgesic concentration of oxycodone for any individual patient may increase with repeated dosing due to an increase in pain and/or the development of tolerance.

Concentration—Adverse Experience Relationships: OxyIR Capsules and OxyFAST CONCENTRATE Solution are associated with typical opioid-related adverse experiences similar to those seen with all opioids. There is a general relationship between increasing oxycodone plasma concentration and increasing frequency of dose-related opioid adverse experiences such as nausea, vomiting, CNS effects, and respiratory depression. In opioid-tolerant patients, the situation is altered by the development of tolerance to opioid-related side effects, and the relationship is poorly understood.

As with all opioids, the dose must be individualized (see **DOSAGE AND ADMINISTRATION**) because the effective analgesic dose for some patients will be too high to be tolerated by other patients.

INDICATIONS AND USAGE

For the relief of moderate to moderately severe pain.

CONTRAINDICATIONS

OxyIR and OxyFAST are contraindicated in patients with known hypersensitivity to oxycodone, or in any situation where opioids are contraindicated. This includes patients with significant respiratory depression (in unmonitored settings or the absence of resuscitative equipment), and patients with acute or severe bronchial asthma, or hypercarbia. OxyIR and OxyFAST are contraindicated in any patient who has or is suspected of having paralytic ileus.

WARNINGS

Respiratory Depression: Respiratory depression is the chief hazard from all opioid agonist preparations. Respiratory depression occurs most frequently in elderly or debilitated patients, usually following large initial doses in non-tolerant patients, or when opioids are given in conjunction with other agents that depress respiration.

Oxycodone should be used with extreme caution in patients with significant chronic obstructive pulmonary disease or cor pulmonale, and in patients having a substantially decreased respiratory reserve, hypoxia, hypercapnia, or preexisting respiratory depression. In such patients, even usual therapeutic doses of oxycodone may decrease respiratory drive to the point of apnea. In these patients alternative non-opioid analgesics should be considered, and opioids should be employed only under careful medical supervision at the lowest effective dose.

Hypotensive Effect: OxyIR® Capsules and OxyFAST® CONCENTRATE Solution, like all opioid analgesics, may cause severe hypotension in an individual whose ability to maintain blood pressure has been compromised by a depleted blood volume, or after concurrent administration with drugs such as phenothiazines or

other agents which compromise vasomotor tone. OxyIR and OxyFAST may produce orthostatic hypotension in ambulatory patients. OxyIR and OxyFAST, like all opioid analgesics, should be administered with caution to patients in circulatory shock, since vasodilation produced by the drug may further reduce cardiac output and blood pressure.

Drug Dependence: Oxycodone can produce drug dependence of the morphine type, and therefore, has the potential for being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration of this drug, and it should be prescribed and administered with the same degree of caution as appropriate to the use of other oral narcotic-containing medications. Like other narcotic-containing medications, this drug is subject to the Federal Controlled Substances Act.

Usage in Ambulatory Patients: Oxycodone may impair the mental and/or physical abilities required for the performance of potential hazardous tasks such as driving a car or operating machinery. The patient using this drug should be cautioned accordingly.

Interaction with Other Central Nervous System Depressants: Patients receiving other narcotic analgesics, general anesthetics, phenothiazines, other tranquilizers, sedative-hypnotics, or other CNS depressants (including alcohol) concomitantly with oxycodone hydrochloride may exhibit an additive CNS depression. When such combined therapy is contemplated, the dose of one or both agents should be reduced.

Usage in Pregnancy: Safe use in pregnancy has not been established relative to possible adverse effects on fetal development. Therefore, this drug should not be used in pregnant women unless, in the judgment of the physician, the potential benefits outweigh the possible hazards.

Usage in Children: This drug should not be administered to children.

PRECAUTIONS

Special Precautions Regarding OxyFAST Oral CONCENTRATE 20 mg/1 mL Solution

OxyFAST 20 mg/1 mL solution is a highly concentrated solution. Care should be taken in the prescription and dispensing of this solution strength. Patients should be instructed against use by individuals other than the patient, as inappropriate use may cause acute overdosage.

General: Opioid analgesics given on a fixed-dosage schedule have a narrow therapeutic index in certain patient populations, especially when combined with other drugs, and should be reserved for cases where the benefits of opioid analgesia outweigh the known risks of respiratory depression, altered mental state, and postural hypotension.

Use of OxyIR and OxyFAST is associated with increased potential risks and should be used only with caution in the following conditions: acute alcoholism, adrenocortical insufficiency (e.g., Addison's disease), CNS depression or coma, delirium tremens, debilitated patients; kyphoscoliosis associated with respiratory depression; myxedema or hypothyroidism; prostatic hypertrophy or urethral stricture; severe impairment of hepatic, pulmonary, or renal function; and toxic psychosis.

The administration of oxycodone, like all opioid analgesics, may obscure the diagnosis or clinical course in patients with acute abdominal conditions. Oxycodone may aggravate convulsions in patients with convulsive disorders, and all opioids may induce or aggravate seizures in some clinical settings.

Interactions with Mixed Agonist/Antagonist Opioid Analgesics: Agonist/antagonist and partial agonist analgesics (i.e., pentazocine, nalbuphine, butorphanol, and buprenorphine) should be administered with caution to a patient who has received or is receiving a course of therapy with a pure opioid agonist analgesic such as oxycodone. In this situation, mixed agonist/antagonist and partial agonist analgesics may reduce the analgesic effect of oxycodone and/or may precipitate withdrawal symptoms in these patients.

Use in Pancreatic/Biliary Tract Disease: Oxycodone may cause spasm of the sphincter of Oddi and should be used with caution in patients with biliary tract disease, including acute pancreatitis. Opioids like oxycodone may cause increases in the serum amylase level.

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Head Injury and Increased Intracranial Pressure: The respiratory depressant effects of opioids and their capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, other intracranial lesions, or a pre-existing increase in intracranial pressure. Furthermore, opioids produce adverse reactions which may obscure the clinical course of patients with head injuries.

Acute Abdominal Conditions: The administration of this drug or other opioids may obscure the diagnosis or clinical course in patients with acute abdominal conditions.

Information for Patients/Caregivers: If clinically advisable, patients receiving OxyIR (immediate-release) Capsules or OxyFAST CONCENTRATE Solution or their caregivers should be given the following information by the physician, nurse, pharmacist, or caregiver:

1. Patients should be advised not to adjust the dose of this drug without consulting the prescribing professional.
2. Patients should be advised that this drug may impair mental and/or physical ability required for the performance of potentially hazardous tasks (e.g., driving, operating heavy machinery).
3. Patients should not combine this drug with alcohol or other central nervous system depressants (sleep aids, tranquilizers) except by the orders of the prescribing physician, because additive effects may occur.
4. Women of childbearing potential who become, or are planning to become, pregnant should be advised to consult their physician regarding the effects of analgesics and other drug use during pregnancy on themselves and their unborn child.
5. Patients should be advised that this drug is a potential drug of abuse. They should protect it from theft, and it should never be given to anyone other than the individual for whom it was prescribed.
6. Patients should be advised that if they have been receiving treatment with this drug for more than a few weeks and cessation of therapy is indicated, it may be appropriate to taper this drug dose, rather than abruptly discontinue it, due to the risk of precipitating withdrawal symptoms. Their physician can provide a dose schedule to accomplish a gradual discontinuation of the medication.

Laboratory Monitoring: Due to the broad range of plasma concentrations seen in clinical populations, the varying degrees of pain, and the development of tolerance, plasma oxycodone measurements are usually not helpful in clinical management. Plasma concentrations of the active drug substance may be of value in selected, unusual, or complex cases.

Use in Drug and Alcohol Addiction: OxyIR and OxyFAST are opioids with no approved use in the management of addictive disorders. Its proper usage in individuals with drug or alcohol dependence, either active or in remission, is for the management of pain requiring opioid analgesia.

Drug-Drug Interactions: The CNS depressant effects of oxycodone hydrochloride may be additive with that of other CNS depressants. See **WARNINGS**.

Opioid analgesics, including OxyIR and OxyFAST, may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.

Oxycodone is metabolized in part to oxycodone via CYP2D6. While this pathway may be blocked by a variety of drugs (e.g., certain cardiovascular drugs and antidepressants), such blockade has not yet been shown to be of clinical significance with this agent. Clinicians should be aware of this possible interaction, however.

Mutagenicity/Carcinogenicity: Oxycodone was not mutagenic in the following assays: Ames Salmonella and E. Coli test with and without metabolic activation at doses of up to 5000 µg; chromosomal aberration test in human lymphocytes in the absence of metabolic activation at doses of up to 1500 µg/mL and with activation 48 hours after exposure at doses of up to 5000 µg/mL, and in the *in vivo* bone marrow micronucleus test in mice (at plasma levels of up to 48 µg/mL). Mutagenic results occurred in the presence of metabolic activation in the human chromosomal aberration test (at greater than or equal to 1250 µg/mL) at 24 but not 48 hours of exposure and in the mouse lymphoma assay at doses of 50 µg/mL or greater with metabolic activation and at 400 µg/mL or greater without metabolic activation. The data from these tests indicate that the genotoxic risk to humans may be considered low.

Studies of oxycodone in animals to evaluate its

cardiogenic potential have not been conducted owing to the length of clinical experience with the drug substance.

Pregnancy: Teratogenic Effects—Category B: Reproduction studies have been performed in rats and rabbits by oral administration at doses up to 8 mg/kg (48 mg/m²) and 125 mg/kg (1375 mg/m²), respectively. These doses are 3 and 47 times a human dose of 160 mg/day (90 mg/m²), based on mg/kg of a 60 kg adult (0.5 and 15 times the human dose based upon mg/m²). The results did not reveal evidence of harm to the fetus due to oxycodone. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nonteratogenic Effects: Neonates whose mothers have been taking oxycodone chronically may exhibit respiratory depression and/or withdrawal symptoms, either at birth and/or in the nursery.

Labor and Delivery: OxyIR and OxyFAST are not recommended for use in women during and immediately prior to labor and delivery because oral opioids may cause respiratory depression in the newborn.

Nursing Mothers: Low concentrations of oxycodone have been detected in breast milk. Withdrawal symptoms can occur in breast-feeding infants when maternal administration of an opioid analgesic is stopped. Ordinarily, nursing should not be undertaken while a patient is receiving OxyIR or OxyFAST since oxycodone may be excreted in the milk.

Pediatric Use: Safety and effectiveness in pediatric patients have not been established.

Special Risk Patients: This drug should be given with caution to certain patients such as the elderly or debilitated, and those with severe impairment of hepatic or renal function, hypothyroidism, Addison's disease and prostatic hypertrophy, or urethral stricture.

ADVERSE REACTIONS

The most frequently observed reactions include light-headedness, dizziness, sedation, nausea, and vomiting. These effects seem to be more prominent in ambulatory than in nonambulatory patients, and some of these adverse reactions may be alleviated if the patient lies down. Many of these adverse events will cease or decrease in intensity as oxycodone therapy is continued and some degree of tolerance is developed. Other adverse reactions include euphoria, dysphoria, constipation, skin rash, and pruritus.

DRUG ABUSE AND DEPENDENCE (Addiction)

Oxycodone products are common targets for both drug abusers and drug addicts.

Drug addiction (drug dependence, psychological dependence) is characterized by a preoccupation with the procurement, hoarding, and abuse of drugs for non-medical purposes. Drug dependence is treatable, utilizing a multi-disciplinary approach, but relapse is common. Isotrogenic "addiction" to opioids legitimately used in the management of pain is very rare. "Drug seeking" behavior is very common to addicts. Tolerance and physical dependence in pain patients are not signs of psychological dependence. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control. Most chronic pain patients limit their intake of opioids to achieve a balance between the benefits of the drug and dose-limiting side effects. Physicians should be aware that psychological dependence may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true psychological dependence and is characterized by misuse for non-medical purposes, often in combination with other psychoactive substances.

MANAGEMENT OF OVERDOSAGE

Signs and Symptoms: Serious overdose of oxycodone hydrochloride is characterized by respiratory depression (a decrease in respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, skeletal muscle flaccidity, odd and clammy skin, and sometimes bradycardia and hypotension. In severe overdosage, apnea, circulatory collapse, cardiac arrest, and death may occur.

Treatment: Primary attention should be given to the re-establishment of adequate respiratory exchange through

provision of a patent airway and the institution of assisted or controlled ventilation. The narcotic antagonist naloxone is a specific antidote against respiratory depression which may result from overdosage or unusual sensitivity to narcotics, including oxycodone. Therefore, an appropriate dose of naloxone (usual initial adult dose: 0.4 mg) should be administered, preferably by the intravenous route, simultaneously with efforts at respiratory resuscitation. Since the duration of action of oxycodone may exceed that of the antagonist, the patient should be kept under continued surveillance and repeated doses of the antagonist should be administered as needed to maintain adequate respiration. An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression.

Oxygen, intravenous fluids, vasopressors, and other support measures should be employed as indicated. Gastric emptying may be useful in removing unabsorbed drug.

DOSAGE AND ADMINISTRATION

Special Precautions Regarding OxyFast Oral CONCENTRATE 20 mg/1 mL Solution

OxyFast 20 mg/1 mL solution is a highly concentrated solution. Care should be taken in the prescription and dispensing of this solution strength. Patients should be instructed against use by individuals other than the patient, as inappropriate use may cause acute overdosage.

Dosage should be adjusted to the severity of the pain and the response of the patient. It may occasionally be necessary to exceed the usual dosage recommended below in cases of more severe pain or in those patients who have become tolerant to the analgesic effects of opioids. This drug is given orally. The usual adult dosage is 5 mg every 6 hours as needed for pain.

Nurse/Patient Instructions: Fill dropper to the level of the prescribed dose (1.0 mL = 20 mg, 0.75 mL = 15 mg, 0.5 mL = 10 mg and 0.25 mL = 5 mg). For ease of administration, add dose to approximately 30 mL (1 fl. oz.) or more of juice or other liquid. May also be added to applesauce, pudding, or other semi-solid foods. The drug-food mixture should be used immediately and not stored for future use.

HOW SUPPLIED

OxyIR® (oxycodone hydrochloride) Capsules:

5 mg capsules, Cap: Boige Imprinted with O-IR; Body: Orange Imprinted with PF 5mg

NDC 59011-201-10: Opaque plastic bottle containing 100 capsules

OxyFAST® (oxycodone hydrochloride) Oral CONCENTRATE Solution:

20 mg per 1 mL

NDC 59011-225-20: High density polyethylene plastic, with child-resistant closure bottle with child-resistant dropper in 30 mL size.

Discard opened bottle of oral solution after 90 days. Protect from light.

Store OxyFAST oral CONCENTRATE solutions and OxyIR (oxycodone hydrochloride) capsules at 25°C (77°F); excursions permitted between 15°-30°C (59°-86°F).

CAUTION

DEA Order Form Required.

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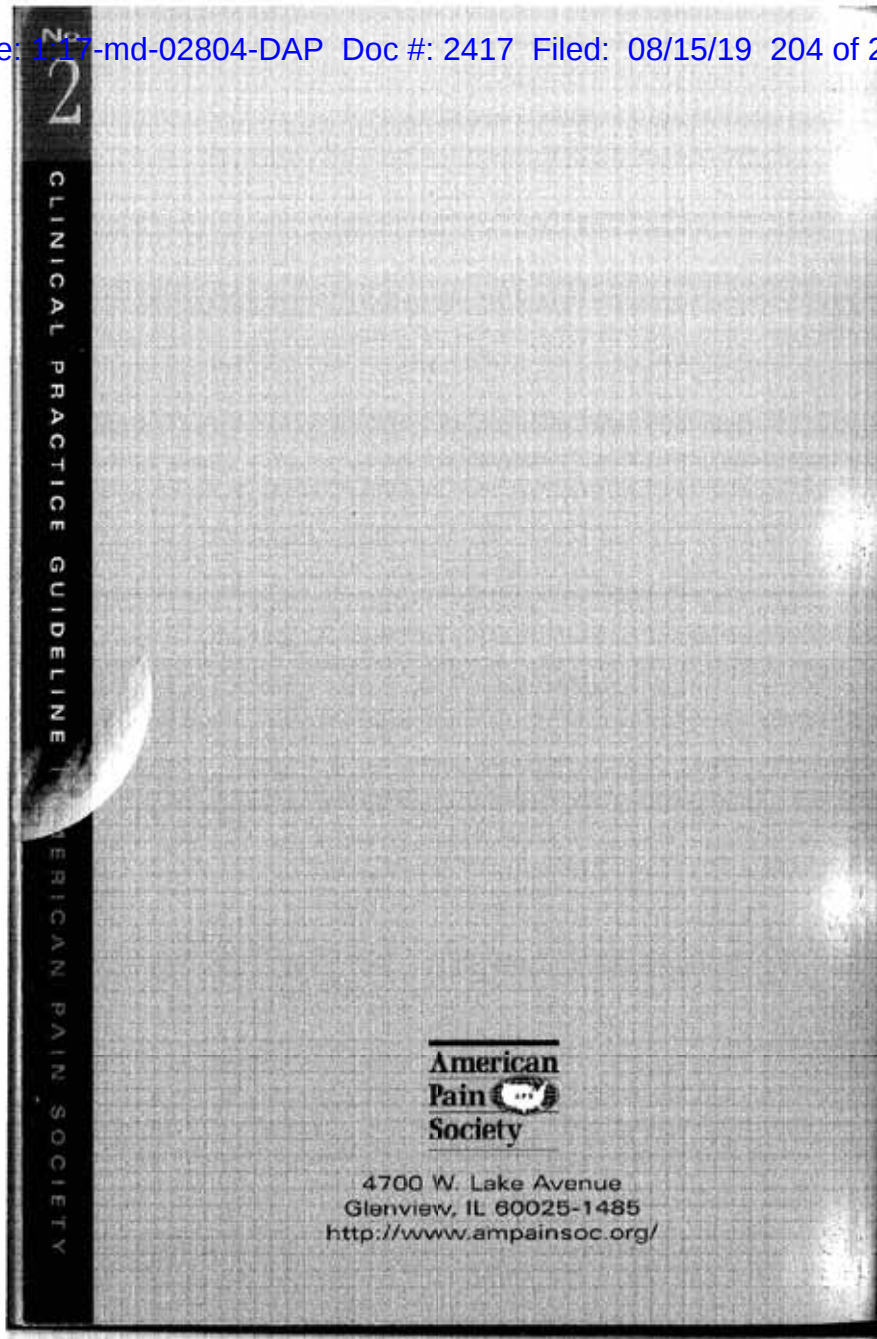
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